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Avian Tubercle Bacilli in Lymph Nodes of Cattle.—Of the cattle tested in Wisconsin during 1935, 0.24 per cent reacted to tuberculin. About 50 per cent of these animals showed tuberculous lesions at autopsy while the remainder showed no visible lesions or only skin lesions. The lymph nodes of 28 tuberculin reacting animals were examined by cultures and guinea-pig inoculation. Three were found to be infected with avian tubercle bacilli, 23 with mammalian tubercle bacilli, and in 2 the results were negative. It was found during the study that coagulated egg medium and potato medium were unsatisfactory for cultivation of bovine tubercle bacilli from tuberculous bovine tissues and from tuberculous guinea-pig tissues. The presence of glycerine was partially responsible for this unsuitability since it has been shown to be bacteriostatic to small inocula of bovine tubercle bacilli. It appears probable that infection with avian tubercle bacilli is responsible for a part of the tuberculin reaction in lesion as well as no-visible-lesion cattle. The ratio of the number of cows reacting because of infection with avian tubercle bacilli to the total number of reactors has been increasing as the number infected with bovine tubercle bacilli has been reduced, and will probably continue to increase until measures are taken to eradicate tuberculosis in chickens and hogs.—*The Presence of Avian Tubercle Bacilli in the Lymph Nodes of Cattle, Janet McCarter, E. G. Hastings & B. A. Beach, J. Am. Vet. Med. Assn., May, 1937, xc, 619.*—(*L. F. B.*)

Tubercle Bacilli in Dairy Products.—Goyal and Obermann in finding a higher percentage of positive findings of tubercle bacilli in milk products than did Edington and Pullinger concluded that the latter investigators used too small an inoculum and too short a period of observation of their guinea pigs. It was noted that all four investigators found tubercle bacilli only in pasteurized milk products. It was wondered if this contamination might not be due to causes subsequent to the pasteurization. In consequence specimens of milk products fresh from the dairy were examined as well as products which had been exposed in markets and in stores. Samples taken from butter and cheese from the surface and from different depths were examined separately. Following the technique of Goyal and Obermann large samples of the dairy products were used and periods of observation were long. Half of a twenty gram sample was inoculated into a guinea pig, the remaining half was cultured on Loewenstein's medium. Several samples fresh from the dairy were found to contain tubercle bacilli of the bovine type. This demonstrated the initial presence of the tubercle bacilli in the dairy products. Out of eleven samples of butter one was found to contain tubercle bacilli on the surface but not in the inner

part of the sample. These same samples were placed in the open market for three days and rechecked. In three samples the surface was contaminated while in the depths of the butter no tubercle bacilli could be demonstrated. Out of ten samples of cheese only one was found to contain tubercle bacilli. That sample had been exposed for a long time in the market. It was an inferior grade of cheese. All specimens of cheese fresh from the dairy were found to be negative for tubercle bacilli. Fourteen samples of cream were examined. One fresh and three exposed samples contained tubercle bacilli. These studies show that contamination of dairy products with tubercle bacilli may take place after they have been marketed.—*Contribution a la recherche du bacille tuberculeux dans le lait, le beurre et le fromage blanc, W. Sarnowieg, Compt. Rend. Soc. Biol., October 17, 1936, cxxiii, 370.*—(*M. T. W.*)

Tubercle Bacilli and Bang's Bacilli in Dairy Products in Salonica.—It has previously been reported that tuberculosis of bovine origin does not exist in Salonica due to the fact that all the milk for human consumption is first heat treated. Further studies were made to determine the presence of tubercle bacilli and Bang's bacilli in raw milk products. Thirty-five pooled specimens of raw milk were examined by cultural methods and by guinea pig inoculations. Specific abortus agglutinins appeared in the animals four to six weeks later. Tuberculin tests made every two weeks after the inoculation were negative. The animals were all grossly negative at autopsy for tuberculous lesions and lesions of brucella infection. Cultures however of four milk samples yielded colonies of acid-fast organisms which proved to be virulent for the rabbit. Ten samples of butter were similarly examined. Animals were all negative for both brucella and tuberculous infections. Two microcolonies of acid-fast bacilli were found on culture which proved to be avirulent. These experiments show that in spite of the prevalence of tuberculous and brucella infections in Salonica there is a great rarity of these bacilli in cow's milk.—*Recherches sur l'existence du bacille tuberculeux et du bacille de Bang dans le lait et le beurre du commerce a Salonique, B. Ananiades & N. Papanarghyrou, Compt. Rend. Soc. Biol., November 21, 1936, cxxiii, 776.*—(*M. T. W.*)

Tuberculin Reactions in No-Lesion Cattle.—The occurrence of no-visible-lesion reactors to tuberculin raised the question whether some agent other than the bovine bacillus was capable of causing sensitization to tuberculin. In 1916 attention was called to certain reactors in which no tuberculosis could be found but which on autopsy showed subcutaneous swelling or nodules, usually on the extremities in which acid-fast organisms could frequently be found. Until recently cultivation of these organisms has been unsatisfactory. In some instances the avian and human tubercle bacillus contributes to these no-lesion cases. There also appear to be other, apparently harmless, acid-fast organisms that are capable of causing sensitization to tuberculin. Studies over the past 15 years seem to rule out *Brucella abortus* as causing sensitization to tuberculin. Seven from a shipment of 42 cattle from the island of Guernsey reacted to tuberculin when landed here but were said to be negative before shipment. Two were examined and no lesions found. Six months later 3 of the remaining 5 had lost their sensitivity. From one of the reactors an organism was recovered by rather devious culture and animal passage and proved to be a pure avian type of tubercle bacillus. A group of 23 cattle were fed and injected with human bacilli 35 years ago. Only 6 of the group failed to react to tuberculin. Usually only one test was positive although at times a local tuberculous abscess persisted. The udder of one cow was infected. The first tuberculin test was positive but remained negative from 1901 to 1912 although human type tubercle bacilli were excreted from the infected udder during the entire period. Six cattle were similarly treated in 1931 and 3 of the 6 gave a positive tuberculin reaction. The following year the tests were negative and at autopsy no lesions were found. Daines has succeeded in obtaining cultures of acid-fast organisms from skin lesions, or the subcutaneous nodules, and two apparently identical acid-fast organisms have been recovered by the author, one from New Mexico and the other from Maryland. Study of these organisms lends support to the possibility that they may be the causal agent in the skin lesions. The organisms caused more of a sensitization to avian than mammalian tuberculin but this does no more than suggest that they may be mutant avian-type organisms. It seems more probable that they are one of the numerous acid-fast organisms present in all soils and they seem to be associated with, but not exactly like, the group II soil organisms isolated by Frey and Hagan. A "tuberculin" made from the skin lesion organism was of little practical use in separation of skin-lesion reactors from tuberculous animals, 11.5 per cent of tuberculous cattle

reacting to it while 75 per cent of skin-lesion cases reacted. With 41 of the 48 states showing an incidence of less than 0.5 per cent of bovine tuberculosis these non-specific reactors are becoming more noticeable and an understanding of them should be had. Cattle are relatively immune to avian tuberculosis but in sections where poultry tuberculosis is very prevalent cattle may become sensitized to it and form a source of disturbance in the cattle testing program. Several reports have been made where one type of organism, avian, has been noticed to change into another type, mammalian, and the pendulum of thought appears to be swinging again toward mutation. Sensitization of cattle by human tubercle bacilli forms a very small portion of the no-lesion type of reactors. In regions where this type of nonspecific reactor is found, it would seem advisable that skin-lesion reactors be marked as suspicious, deferring judgment until a retest several months later may be compared with the first test.—*Tuberculin Reactions in Cattle Showing No Visible Tuberculous Lesions on Postmortem, A. B. Crawford, J. Am. Vet. Med. Assn., November, 1936, lxxxix, 562.*—(*L. F. B.*)

Susceptibility of Chickens to Tuberculosis.—Twenty-nine apparently normal hens, 10 Barred Rocks and 19 White Leghorns, were added to a flock of 30 hens that had previously reacted positively to intracutaneous injections of avian tuberculin. All the chickens were approximately 18 months of age. They were maintained in an unhygienic environment to provide optimal conditions for spread of the disease. Three weeks after the experiment was begun, and at irregular intervals throughout the course, intracutaneous tuberculin tests were made. In 18 of the 30 positive hens part or all of the spleen was removed under general anaesthetic to demonstrate the presence of tuberculous lesions. Of the 30 positively reacting hens, tuberculous lesions were demonstrated in 18. Although no gross or microscopic lesion was found in any of the remaining twelve, a culture of the spleen from one, 156 days prior to death, was positive for tubercle bacilli. Ten of these birds died during the first 100 days, 9 lived more than 100 days, 4 more than 200, 2 more than 400, and 1 more than 500 days. Of the 29 apparently normal hens, 7, or 24 per cent, had lesions of tuberculosis at necropsy. One of the 7 hens gave a positive tuberculin reaction and it showed extensive lesions at necropsy. One of the seven was a White Leghorn and 6 were Barred Rocks. The reliability of the tuberculin test is not impugned by these findings and the failure to obtain a positive reaction in the 6 chickens may be accounted for by the excessive and repeated infection followed by extensive progression of the disease. It is indicated that, under the conditions of the experiment, the majority of the chickens were capable of withstanding an environmental exposure to tuberculosis for a considerable period without lesions of the disease developing.—*Susceptibility of Chickens to Tuberculosis Following Spontaneous Exposure to the Infection, W. H. Feldman, J. T. Bollman & F. C. Mann, J. Am. Vet. Med. Assn., November, 1936, lxxxix, 551.*—(*L. F. B.*)

Pulmonic Alveolar Epithelium.—The presence or absence of a continuous epithelial lining of the adult pulmonary alveolar wall was discussed. Dr. J. L. Bremer conceived the alveoli as being lined by a continuous epithelial layer of entodermal origin whose unit is a cell with a relatively thick body from which a thin film of flange extends over the pulmonary capillary. The cell rests upon a thin layer of connective tissue. Dr. D. M. Palmer agreed that in the early stage the future alveoli have a continuous lining but that during the twenty-first week of foetal life the epithelium changes. The weakly staining cytoplasm became loaded with birefringent lipoid material while the nuclei appeared vesicular. At the same time young capillary loops pushed in between the changed epithelial cells and displaced them. Dr. W. Bloom was unable to find irrefutable evidence of a continuous epithelial lining and regarded various methods used for demonstration as unreliable or capable of other interpretation. Alveolar phagocytes may be of dual origin, entodermal as well as mesodermal. No cuboidal or flattened epithelium is visible in the alveoli of experimentally collapsed lungs. Dr. D. H. Sprunt pointed out that alveolar lining cells become apparent in certain morbid conditions and have the morphology and staining characteristics of epithelium. Dr. B. M. Fried failed to find evidence of an epithelial lining Large mononuclear alveolar phagocytes are of mesodermal origin and develop only from the alveolar septums. No conclusions were reached by the conference. If no alveolar epithelium exists there must be a free edge of epithelium somewhere along the bronchial tree. The old idea of a nonnucleated plate as a component of alveolar lining is disappearing. The apparent rise to predominance of the view that no alveolar epithelium is present, because of inability to demonstrate it, would mean the recasting of physiological

and pathological thinking on the alveolus. Exudates in the alveoli would technically be inside the body.—*Pulmonic Alveolar Epithelium, A Round Table Conference, C. C. Macklin, J. Thoracic Surg., October, 1936, vi, 82.*—(*L. F. B.*)

Pathogenesis of Tuberculosis.—The first infection is usually by inhalation and the first focalization is in the lung. This infection causes two potentially permanent alterations in the host: it produces allergy and it establishes within the body a deposit of tubercle bacilli. Which mode of reinfection, endogenous or exogenous, is predominant is a vexing question; it is the central problem in the pathogenesis of pulmonary tuberculosis in the adult. It is also the all important question for the epidemiology of the disease. The opinion that favors exogenous reinfection is based essentially on statistical work, comparing contact and noncontact groups. However, the groups examined are usually slum populations. The mere fact that painstaking epidemiological studies are necessary to prove the greater frequency of clinical disease in contact than in noncontact groups is a strong argument against the predominating importance of exogenous reinfection. The school that denies the possibility of exogenous reinfection depends on the results of animal experiments. With extremely careful dosage of first and secondary infection, it can be shown that a practically complete immunity against exogenous reinfection may be developed in infected animals. But such optimal conditions do not occur in human life. The fact that exudative and productive lesions are commonly found in the same lung in close proximity shows at once that one single factor, such as allergy, is totally inadequate to explain the two essentially different tissue reactions. The essentials that are known of allergy in tuberculosis can be expressed in two statements: Allergy can be produced only by infection with (living or dead) tubercle bacilli. Allergy accentuates and hastens the native tissue reactions against tubercle bacilli. The first focalization of bacilli occurs as a rule in the parenchyma of the subpleural layers of the lung, relatively rarely in the apex. The earliest lesion is a tuberculous pneumonia, which soon becomes surrounded by proliferative tissue changes from which a dense fibrotic capsule develops around the centre, which in turn undergoes caseation and calcification. Simultaneously or later the mediastinal lymph nodes become involved; they, then, show more or less completely the same retrogressive changes as does the parenchymal lesion. The most frequent development of this primary complex is retrogression and calcification without clinical disease. In some cases the parenchymal focus may progress by contiguous spread, causing extensive caseous pneumonias and excavations. More frequently the parenchymal focus heals while the lymphoglandular focus smolders on, discharging at intervals bacilli into the lymph and blood-stream; they may focalize anywhere in the body, causing bone lesions, urogenital disease, scattered lobular pneumonic foci usually in the upper portions of the lungs; or, if a massive discharge of bacilli occurs, the result may be a generalized miliary tuberculosis. The borderline between the period of primary infection and that of the early disseminations is too blurred to permit, as has been suggested, a differentiation into a primary and secondary stage. Following the more or less complete healing of the primary complex or subsequent to major or lesser manifestations of early dissemination, a latent period usually intervenes before tuberculosis in the adult develops. The pulmonary tuberculosis of adult life begins usually with a single, exudative focus. There are essentially three mechanisms by which this focus may develop: (*1*) A bronchogenic spread occurs from incompletely healed apical lesions. (*2*) Bacilli from an active primary lymph node focus are carried into the blood-stream and are filtered out in the lung. (*3*) Bacilli are inhaled from the outside. The early lesion is a tuberculous pneumonia, seen most frequently in the subapical region. This lesion is always unstable; it soon progresses or retrogresses. If a cavity develops, a source of bacillary dissemination is established, from which at any time new bronchogenic spread may occur. From this point on, localized destructive lesions constitute the main character of the disease. Within the lung this means bronchogenic spread, and beyond it, it means laryngeal and intestinal tuberculosis. The natural course of progressive pulmonary tuberculosis is, then, a series of bronchogenic tuberculous lobular pneumonias, which may heal or progress, fibrose or excavate. The patient may finally die from progressive destruction of parenchyma, or from the crippling tissue alterations that healing brings about. Tuberculosis may heal spontaneously at almost any phase of its development; the exceptions are (*1*) massive blood-stream infections, (*2*) focalization in vital regions (for example, the fourth ventricle) and (*3*) large excavations with hard, fibrosed walls. In order of frequency, spontaneous healing takes place (*1*) in the primary complex, (*2*) in mild early dissemination,

(*3*) in the early infiltrate.—*Pathogenesis of Tuberculosis, M. Pinner, J. Am. M. Assn., August 15, 1936, cvii, 475.*—(*G. L. L.*)

Primary Complex in Tuberculosis.—Parrot, in 1876, in a brief note expressed his views as follows: "Whenever a bronchial node is the seat of a tuberculous lesion there exists an analogous lesion in the lungs (*adénopathie similaire*) . . . The alterations in the lymph nodes are usually more extensive than those of the corresponding pulmonary parenchyma (law of Parrot)." When Parrot first related his findings, their significance was not appreciated by him or by his contemporaries; the observation was looked on as merely theoretical. George Küss, in 1898, was the first to make an extensive study of this subject and to interpret fully its significance. He thereby discredited the belief that tuberculosis is a hereditary disease transmitted from mother to foetus via the placenta, and produced convincing evidence to show that the disease is acquired as a rule postpartum by inhalation of Koch's bacilli—an aerogenous infection. He further ascertained the type, the constancy and the pathognomonic character of the primitive lesion (*le foyer pulmonaire primitive*) which he described as a minute subpleural tuberculous granuloma accompanied by tuberculosis of the tracheobronchial lymph nodes. This he designated as *chancre d'inoculation avec adénopathie similaire.* The Austro-German pathologists were quick to grasp the far reaching importance of this study. H. Albrecht corroborated Küss's findings from the study of a large autopsy material. However, not until Ghon published his monograph in 1912 did the teaching of Küss become common knowledge. The article by Ghon was so imposing as to give the impression that he was the originator of this conception; hence the misnomer "Ghon tubercle." In justice to Ghon it must be stated that he gave full credit to Küss for this remarkable observation.—*The Primary Complex (Initial Anatomic Lesion in Childhood Type of Tuberculosis), A Historical Study, B. M. Fried, Arch. Path., December, 1936, xxii, 829.*—(*J. S. W.*)

Vagosympathetic Balance and Tuberculosis.—Studies of the oculo-cardiac reflex have been made in tuberculous individuals. The R.O.C. was observed to rise several points just prior to the menses. This is the time when haemoptysis and focal congestion have been so frequently observed to occur. With the onset of the menstrual flow the R.O.C. returns to its previous base line. The R.O.C. rises during a period of from two to three hours following meals. This is especially true at times of pulmonary instability. Besides these two physiological excitants to an increased R.O.C., slight focal congestion, a simple cold, and bronchitis can produce this effect. Atmospheric conditions also effect the R.O.C. It has been observed in patients that where one or two of these factors acting simultaneously are not sufficient to produce a haemoptysis the addition of a third may. The R.O.C. is regularly inverted in the tuberculous subject. In one case, that of a medical student, the R.O.C. was taken while the subject was in perfect health and prior to the onset of a pulmonary tuberculosis. It was 70−65 −5. It was again taken three months following the appearance of a rather acute process. The R.O.C. had become 58−61 +3, and 73−78 +5. This change from −5 to +5 is well beyond the limits of error of this test. Other cases were observed in which a minus R.O.C. became plus when the tuberculous process had subsided. The R.O.C. was observed in a long standing case to rise from its usual slight elevation of +2 to +6 during a period when there was clinical evidence of slight increase in activity of the tuberculous process. Cases which evidence a good resistance are those in which the R.O.C. shows the least fluctuation. Cases with progressively downhill courses showed the greatest sensitiveness to atmospheric disturbances, the R.O.C. rising from 15 to 20 points at times. Thus there is reason to believe that the lability of the R.O.C. is of some prognostic significance. One exception is to be noted; in cases where there is an overwhelming toxaemia the R.O.C. may be completely abolished, or there may be a fleeting decrease in the pulse rate. Attention is called to the work of Maignon who made studies of the changes in pulse rate produced by pilocarpine and by atropine in various animals. He found that those animals who had the least resistance to tuberculous infection responded by a decrease in pulse rate following the administration of pilocarpine greater than was the increase following atropine. The converse was also observed.—*Système vago-sympathique et tuberculose, J. Chaize, Arch. Med. Chir. l'App. Resp., 1936, xi, 392.*—(*C. L. D.*)

Bronchospirometry.—This procedure was developed by Jacobaeus as a result of attempts to separate the sputum from the two lungs in pulmonary tuberculosis, in which he used different colored dyes, without conspicuous practical success, especially in cases with copious sputum. During the experiments it occurred to him that it

might prove valuable to separate bronchoscopically the air of the two lungs and in this work he had the collaboration of Liljestrand, a physiologist, and Frenckner, a bronchoscopist. His assistant, Björkman, carried out the spirometric determinations. Two bronchoscopes are used, one introduced into one of the main bronchi, generally the left, which runs for a longer distance without branching, while the second ends in the trachea. Both ends are surrounded by rubber cuffs of the Pflüger type, shutting the air from each lung off efficiently. The other ends are connected with separate Krogh spirometers. The respiratory movements are recorded simultaneously and compared. Bronchoscopy is done under 2 per cent procaine anaesthesia and without pain, merely a sensation of discomfort and suffocation. More than 150 tests have been carried out without accident other than an occasional brief rise of temperature. Carbon dioxide elimination is determined during the tests. Ten normal cases were tested, all medical students attached to the clinic. It was found that the right lung normally has a somewhat larger share in respiration, 53 to 56 per cent, the left 44 to 47 per cent. Tests in different postures showed the lower, rather than the upper lung to breathe more, the difference in respiration and oxygen intake amounting to an average of 10 per cent. Thirteen pathological cases are cited in detail. One woman of 41 with an advanced unilateral right sided tuberculosis and a huge cavity showed an oxygen absorption of only 25 per cent on the right side, a carbon dioxide elimination of 39 per cent, and a ventilation of 43.6 per cent. Air probably passed in and out of the cavity without oxygenation. In another severe case, with predominantly right-sided involvement, there was only 7.3 per cent oxygen intake in the right lung and CO_2 elimination was 22.7 per cent, with ventilation 26.3 per cent. This indicated the right lung to be practically useless functionally. In another severe left-sided case, a young woman of 23, with multiple cystic cavities, oxygen absorption was practically zero and CO_2 elimination and ventilation about 5 per cent on the left. Two patients with extensive right thoracoplasty showed very marked diminution of oxygen absorption but one showed a ventilation of over 24 per cent. Three patients with artificial pneumothorax, one of which had been bilateral and complicated by pleural exudates, showed considerable variation in functional values, which, while not always as expected, were thought to have been of practical value in deciding on further measures, for example, thoracoplasty. As a rule the collapsed lung showed less than 20 per cent of total ventilation. One patient who had a left phrenic evulsion showed a ventilation on that side of only 7.3 per cent. Another patient, with a badly diseased left lung due to bronchiectasis, and shrinkage, showed a ventilation on that side of only 3.5 per cent, and oxygen absorption of 1.5 per cent. Björkman has found that CO_2 elimination accurately follows ventilation but oxygen intake deviates considerably. Oxygen absorption is first affected and less well maintained in advanced disease. He also found cough to be very ineffective in diseased lungs.—*On Bronchospirometry, H. C. Jacobaeus, Brit. J. Tuberc., July, 1936, xxx, 114.*—(*A. P.*)

Abdominal Tension and Pulmonary Function.—The authors made experiments with animals to study the influence of abdominal conditions upon intrabronchial and intrapleural pressure. A bronchoscope was introduced, small hollow copper tubes were inserted into the lower bronchus on each side and were arranged by means of interchangeable tips to occlude the bronchus except for its connection with the lumen of the tube. Rubber tubing was connected to the tubes and, by means of a tambour and lever, records on a moving drum were made. Measurements of intratracheal, intrapleural, and intraäbdominal pressures were recorded following cough under varying conditions. For determination of intrapleural pressure two large, number-fourteen, needles were inserted into both pleural cavities, connected to water manometers, and records made upon the moving drum. To record the pressure within the abdominal cavity, a rubber tube with a small balloon attached to its end was introduced through the oesophagus into the stomach. This was connected to a mercury manometer, and the balloon distended by air pressure to ten millimetres of mercury. The effect of both costal and abdominal types of breathing was recorded. To study the effect of abdominal conditions upon the ejection of fluid from the lower bronchi, X-ray studies were made to learn the time necessary to discharge from the lungs oil opaque to the X-rays. Since abdominal tension and adaptability of the abdominal wall are dependent upon an intact neuromuscular mechanism, the abdominal muscles were resected in some animals. In others, nerve section of the anterior roots from the fourth thoracic to the sixth lumbar was performed. In such animals a marked distention of the abdomen occurred. From this group of experiments one factor appears to be clearly established; the abdominal pressure cannot

function normally in animals with lax abdominal walls. Although abdominal pressure under such conditions does not vary greatly, its effect on thoracic function is altered or lessened. This was particularly apparent following cough. Sustained coughing cannot be induced in animals with weakened abdominal walls. The experiments suggest that from the standpoint of effective respiration and of pulmonary drainage there is an optimum position of the diaphragm. Since this is dependent, among other factors, upon abdominal tension, any change in pressure within the abdomen may influence pulmonary function. For optimum drainage from the lower portions of the lung a low position of the diaphragm is essential. During cough this permits a more positive expiratory bronchial pressure. The low position, however, appears to be conducive to less effective respiration, as shown by a decreased negative intrapleural pressure with normal or forced breathing. This clinically resembles the state of emphysema with low diaphragm and a diminished negative pressure. A high position of the diaphragm appears to be conducive to fair respiratory function, as indicated by a more negative intrapleural pressure, but is less effective from the standpoint of lung drainage, as judged by the time necessary for the expulsion of opaque oil from the bronchus.—*The Influence of Changes of Abdominal Tension upon Pulmonary Function, W. B. Kountz, L. Gottlieb & R. King, J. Clin. Invest., November, 1936, xv, 601.*—(*G. L. L.*)

Bronchoconstrictor Action of Adrenalin.—Bronchoconstrictor action of adrenalin is a rare event. In over 100 experiments on dogs, adrenalin in doses of 2 gamma and upwards almost invariably produces bronchodilation especially when the bronchi are constricted by pilocarpine, acetylcholine, histamine, or ergotoxine. In not more than three experiments has a bronchoconstrictor effect been noted, and then only in amount sufficient to reduce the tidal air by 2 per cent or less. In experiments with isolated perfused lungs in which pituitrin, pitressin or pitocin had been injected, it was found these extracts reversed the usual bronchodilator action of adrenalin to bronchoconstrictor. The bronchoconstrictor action of adrenalin following the administration of extracts of the posterior lobe is reversed by ergotoxine so that adrenalin produces its normal bronchodilator action in ergotoxinized and pituitrinized preparations.—*A Broncho-Constrictor Action of Adrenalin following Injections of Pituitrin, Pitocin or Pitressin in Isolated Perfused Lungs, I. de Burgh Daly, E. G. L. Mark & Barbara Petrovskaia, J. Physiol., March, 1937, cxxxix, 260.*—(*A. E. M.*)

Measurement of Cardiac Output.—Most of the work on cardiac output in recent years has been done by Grollman's acetylene method. This method gives lower results than those obtained by the CO_2 method of Douglas and Haldane. No investigation of the cause of this discrepancy has been carried out. The output of the heart per beat must be a definite quantity though variable and subject to physiological control. "Circulation rate" on the other hand is an expression which has no definite meaning. Any given corpuscle may at one time traverse an extremely short course before returning to the heart, at another time a much longer course. Mixed venous blood returning to the heart must be composed of many fractions which have traversed courses of very variable length and taking very variable times. No measurement of the "circulation rate" by a foreign gas method can therefore be expected to give a wholly accurate measure of the output of the heart since the necessary experimental procedure takes a time which at the best must be expected to exceed the circulation time of some of the blood returning to the heart. Hence any method of measuring the output of the heart by observation of the amount of a foreign gas absorbed by the blood passing through the lungs in a given time must give results which are less than the true figures. This objection also applies to the CO_2 method but this effect is less than in the foreign gas method owing to the shorter time taken by the experimental procedure. The acetylene and venous CO_2 methods were carried out alternately on the same subjects in as short an interval as possible. Also determinations were carried out by a combined method with a view toward reducing the time taken by the acetylene method to that needed for the CO_2 method and of getting simultaneous and not alternate measurements by the two methods. There was close agreement between the two methods, although the agreement was closer when the two methods were run simultaneously by the combined method. However one subject gave discordant results even with the combined method. This discrepancy was explained by the individual variations in the CO_2 content of the mixed venous blood caused by the deep breathing and possibly the effect of CO_2 on the circulation. It is concluded that both methods are liable to error owing to return of blood to the heart before the experiment is completed, and that this error is slightly greater with the

acetylene method as usually performed, the difference decreasing, however, when the total experimental times approach each other.—*Measurement of the Cardiac Output in Man, A. M. Cooke & J. G. Priestley, J. Physiol., June, 1937, xc, 104.*—(*A. E. M.*)

Changes in Lung Volume.—Attention is called to the concept that the lung is not simply an elastic organ which is capable only of contracting. A collapsed lung will actually expand on stimulation of the vagus nerve. This change in tonus and hence potential and real volume of the lung must be considered of importance in collapse therapy for pulmonary tuberculosis. It probably explains certain instances in which the rate of absorption of the air in a pneumothorax apparently undergoes considerable variation. Also the occasional rather marked changes in the size of a cavity in an uncollapsed lung may depend upon this factor.—*Les variations de volume du Poumon à l'état pathologique et à l'état normal, F. Dumarest, Arch. Med. Chir. l'App. Resp., 1936, xi, 161.*—(*C. L. D.*)

Mechanism of Retraction of Lung.—Studies of the elasticity of individual excised lobes of the lungs of dogs indicate that the upper lobes approach more nearly an ideal elasticity than the other lobes. The next in order is the left lower lobe, followed closely by the right middle lobe; the least elastic being the right lower lobe. In the tuberculous lung the factors of sclerosis and increased elasticity favor selective collapse. The involved area does not expand under the influence of atropine in the way healthy lung tissue does. This would lead one to believe that there is a nervous factor as well. By the use of atropine a healthy lobe which was collapsed anteriorly in the presence of a therapeutic pneumothorax was observed to reëxpand. Pneumographic studies in this case indicated that relaxation of bronchial spasm was not the mechanism of action of the drug, also any pulmonary vasomotor dilatation produced by the atropine would be expected to increase rather than decrease congestion and exudation in the small bronchioles. The weight of the tuberculous lesion probably plays only a passive rôle in selective collapse.—*Mécanisme de la rétractilité lobaire dans le poumon sain et pathologique, H. Warembourg & R. Swynghedauw, Arch. Med. Chir. l'App. Resp., 1936, xi, 354.*—(*C. L. D.*)

Mineral Content of Tuberculous Foci.—Previous work employing the tissue-ash technique has demonstrated great differences in the mineral constituents of sections made from abscesses as compared with those from areas of necrosis. The salt content of tissue undergoing nonspecific necrosis consisted chiefly of insoluble calcium salts and sodium phosphate. Alkali carbonate could not be demonstrated in necrotic tissue which had no nuclear content. The soluble salts were decreased in early necrosis and increased in the later stages. In spite of the great increase in ash content no calcification could be demonstrated by histological methods. Studies of the ash content of tissue taken from abscesses or infiltrative processes indicated that there had been an increase in soluble salts even greater than that found in the late stages of necrosis. This was chiefly due to a large amount of alkali carbonate. There was an increase in calcium carbonate and a decrease in the insoluble calcium salts. In necrotic areas where there had been a liquefaction of tissue by leucocytes there was less calcium salt present, but alkali carbonate could be demonstrated. It appeared that the mineral constituents of the ash were determined by the nature of the tissue, and the nuclei were apparently the source of the calcium. Tissue from various organs from the body of a three year old boy dying of miliary tuberculosis was studied by the ash technique. Total ash studies of sections from the liver revealed a uniform salt content in the sections. The structure of the liver and of the tubercles was well seen. There was less ash in the centres of the larger nodules with caseation than in their peripheries. Preparations extracted with water showed less ash in the nodules than in the surrounding liver tissue, but their centres were more dense than their peripheries. It was in the latter regions that the giant cells, epithelial cells and round cells were located. The ash content of the centres was less than appeared in the peripheries in the unwashed preparations. The small tuberculous foci stained a light blue, but somewhat later than did the ash of potassium droplets. Still later and at a time when the ash of sodium bicarbonate droplets was stained, the intensity of the staining of the tubercles was increased. The ash of the liver tissue also took on a blue-green color. Especially striking were the foci that had necrotic centres. The latter stained less intensely than the peripheries. With Stain II the foci were a deeper color. Stain III which stained the ash of sodium phosphate droplets blue, gave to the whole section a uniformly bluish tint. From the above it may be concluded that relative to normal liver tissue there is an increase in the alkali

carbonate and a decrease in the calcium in tuberculous foci. In tuberculous foci with necrotic centres there is more calcium in these areas of early necrosis than in the peripheral tissue, but the calcium content is considerably less than that of the surrounding liver substance. Ash studies of the normal spleen showed that the splenic follicles which are rich in nuclei contain more soluble salts than the pulp which has a higher calcium content. In general, necrotic areas which are rich in nuclei have a greater amount of soluble salts than those poor in nuclei. Studies were also made of various stages of tuberculous caseation and calcification. Early caseous necrosis, as represented by the caseous centres of miliary tubercles, was found to present a thin layer of calcium salts. Calcium carbonate and calcium phosphate were demonstrable, but the alkali carbonate was greatly diminished. In instances of long standing caseation the content of calcium carbonate and calcium phosphate was greatly increased. In old caseous areas there was a marked accumulation of calcium salts. This calcium, however, could not be demonstrated by staining with haematoxylin. In many caseous foci in various organs there was a centre with a dense accumulation of salts. These were not only calcium carbonate but also calcium phosphate. Such areas, if free of nuclei, gave no evidence of the presence of alkali carbonate. Sodium phosphate was always demonstrable in the caseous material. The centres which had a high calcium phosphate content appeared to be the seat of early true calcification. This seemed to represent the transitional stage in the process. Calcium is apparently bound to the necrotic protein in part by adsorption and in part chemically. How this later leads to the great deposition of calcium and true calcification and bone formation is not clear. These studies also indicated that the richer in nuclei a tissue is the more alkali carbonate, especially potassium carbonate, it will contain. Further, in young connective tissue (tuberculous granulation tissue) the salts are chiefly soluble and are present as alkali carbonates especially potassium carbonate. In granulation tissue which is imbedded in connective tissue there is an increase in the percentage of calcium salts in the alkali carbonate.—*Untersuchungen über den Mineralstoffgehalt tuberkulöser Herde mit Hilfe der Schnittveraschung, W. Klostermeyer, Virchow's Arch., December 23, 1936, ccxcviii, 298.*—(*C. L. D.*)

Intracerebral Inoculation of Tubercle Bacilli as a Standard Method.—The irregular course of the disease has long been a serious difficulty in experimental tuberculosis. Even with a standard dose survival time may vary tremendously in different experiments. The present article discusses a method of standardizing infection by the proper use of the intracerebral route of inoculation. Guinea pigs were used throughout and young animals weighing about 400 gm. were found to be most suitable for the trephining operation as the skull bones were soft enough to readily permit this. The method of intracerebral inoculation is as follows: Under full ether anaesthesia and using aseptic procedures, a longitudinal incision, about 8 to 10 mm. long, is made in the skin about 3 mm. to the left of the midline. At a point in this plane not exceeding 4 mm. posterior to a line connecting the posterior commissures of the eyes, the skull is trephined. The instrument used is a no. 60 carpenter's drill fixed in a hollow-handled pin vise, the drill being so fixed in the chuck of the vise that the latter prevents penetration beyond the desired point. The injection is made with a tuberculin syringe, using a fine needle, the amount injected being 0.1 cc. Closure of the skin incision is made with a single metal clip. The animals regain consciousness within a few minutes, and, beyond being a little listless, show no untoward effects. The hazard from the method itself is small either from operative trauma or extraneous causes. The animals were allowed to die or were chloroformed when in extremis. The animals were examined in gross and sections of the brain and spleen and occasionally other tissues were examined as routine for the presence of bacteria and the degree of histological changes. In the first experiment three groups of four guinea pigs received avian, bovine and human tubercle bacilli respectively. The dose of each organism was 0.15 mgm. suspended in 0.15 cc. of either saline or mucin. The animals inoculated with avian organisms survived from 11 to 49 days, those receiving bovine bacilli from 10 to 13 days and those receiving human bacilli lived from 17 to 19 days. The mucin did not appreciably alter the survival time in any instance. With mammalian organisms, animals inoculated with the same dose of the same strain survive approximately the same number of days. Experiments were then done with much smaller doses of mammalian organisms. A large group of guinea pigs received human and bovine bacilli in the following doses given intracerebrally: 0.1, 0.001, 0.000,01 and 0.000,001 mgm. By this simple titration it was hoped that an end-point of

dosage would be reached at which some animals would survive. Another smaller group of guinea pigs were inoculated intracerebrally with graded doses of H37 human tubercle bacilli suspended in serum, either normal horse or normal rabbit serum. It was found that the body temperature was the best index of the condition of the animal at any period of the disease. On the first or second day after inoculation it was usually elevated to 103° or 104°F. Thereafter the temperature was normal or nearly so for a few days followed by a gradual rise to a peak of 105° to 106°F. No symptoms were usually noted until the time of the highest fever. After the peak the temperature gradually declined with a concomitant increase in symptoms. During the last 24 hours of life the temperature was subnormal, sometimes markedly so. With diminishing doses of organisms, all phases of the temperature curve were prolonged except the original postinoculation rise. The first noticed clinical symptom was listlessness followed by abnormal gait and later often paralysis. Convulsions were noted in many of the animals at the terminal stage, also stupor. Pathologically the brain and cervical lymph nodes were invariably found involved. The spleens usually showed a few pinpoint tubercles. Pulmonary lesions were minimal in extent and always microscopical. Perhaps the most important features of the disease produced by intracerebral inoculation of tubercle bacilli were its acuteness and the uniformity of survival time in comparable animals. All the experiments were completed in a relatively short time as practically all animals succumbed at the end of 5 weeks except those receiving minimal dosage when an occasional one survived. The important fact was that all animals receiving a given dose of a given strain of bacilli survived approximately the same number of days. For example, of the animals receiving the bovine strain, those inoculated with 0.1 mgm. died in 11 to 15 days, those with 0.001 mgm. died in 19 to 22 days, those with 0.000,01 mgm. died in 22 to 32 days, and of those with 0.000,001 mgm., three died between the 30th and 36th day, while one survived. Comparable results were obtained with the human strains of tubercle bacilli. The prolongation of the incubation period, and of the disease itself, brought about by diminishing doses, is such that a one-hundredfold dilution of dosage allowed an increase of 4 to 7 days in the survival time. The dose of 0.000,001 mgm. was found to be near the end-point of virulence for mammalian strains of bacilli. In the first experiment the time of death was very irregular in the case of the four animals inoculated with avian organisms, namely from 11 to 49 days. However, the susceptibility of guinea pigs to infection with the avian type bacilli is very low. The suspension of the inoculum (H37) in serum in one of the later experiments gave results closely approximating those in which the bacilli were suspended in saline. For control purpose three small groups of guinea pigs were inoculated intracerebrally with virulent, attenuated and killed tubercle bacilli respectively. The animals receiving the virulent strain soon died, those receiving avirulent strains either survived or died later and the ones getting dead bacilli remained well. From this it is evident that the clinical course and the fatal issue are brought about by the properties of virulence associated with the inoculated bacilli. The results obtained by the methods described have many advantages. First, the acuteness of the disease is such that experiments are terminated rather quickly with consequent considerable saving in time, and in cost of animal maintenance. A fatal result is obtainable with sufficiently small doses of organisms that the method gives promise of service as a test of prophylactic or therapeutic measures. But finally and most important of all is the fact that the infection induced by intracerebral inoculation of tubercle bacilli in guinea pigs is standardizable, and therefore permits the performance of quantitative titration experiments. The results of such experiments, expressed in terms of survival time, should be readily applicable to statistical methods of analysis. —*The Standardization of Longevity against Dose in Experimental Tuberculosis by Intracerebral Inoculation* (*with three plates*), *K. C. Smithburn, J. Exper. Med., November 1, 1936, lxiv, 771.*—(*J. S. W.*)

Experimental Early Pulmonary Tuberculosis of the Adult Type.—This is to be clearly differentiated from primary or "childhood type" pulmonary tuberculosis, designated by American authors, which is obviously caused by inhalation infection and may develop into acute generalized tuberculosis where resistance is insufficient, either among children or adults. There is a dispute as to whether the first foci of chronic isolated pulmonary tuberculosis are directly due to exogenous reinfection, the result of haematogenous metastasis, or the result of coarse bronchogenic aspiration from recrudescent foci, that is, "endogenous reinfection." In the experiments here cited, Pagel produced lesions in rabbits characterized by limitation of the process to the lungs, restriction of haematogenous foci to certain areas, especially

the apex, and by the formation of focal confluent infiltrations with a tendency to liquefaction and multiplication by bronchogenic spread. About 70 rabbits were infected by intravenous or intratracheal injection of 0.1 to 0.5 mgm. of BCG or human strains from sputa. Six weeks after the last injection these animals were reinfected, some intravenously, others intratracheally, with 0.001 to 0.01 mgm. of a virulent bovine strain of which 0.01 mgm. killed a normal rabbit in about forty days after intravenous injection. Some were reinfected with human strain H37 which killed a normal animal in about forty days when injected intravenously in doses of 0.1 to 1 mgm. In normal animals intravenous injection of sputum and BCG produced either no macroscopical foci or a fine miliary dissemination appearing within two weeks and absorbing in two or three more weeks, while intracheal injection caused almost negligible lesions in the lower lobes which varied as to persistence or disappearance. Intravenous injection of the virulent strain consistently resulted in extensive generalized tuberculosis with miliary or coarser caseous foci in lungs and kidneys, spleen, and usually also in the liver. A similar intratracheal injection produced a few rather small foci in the lung especially the base, and a slowly progressive tuberculosis, with small foci, in the kidneys and spleen. The severe generalized tuberculosis resulting from virulent intravenous infection was considerably modified in animals previously infected with BCG or human strains. These experiments seemed to prove that intravenous or intratracheal infection with human or BCG strains can confer immunity against virulent reinfection. The picture of "discrete apical miliary tuberculosis" and its sequel of localized fibrosis, and also of "infraclavicular infiltrate" could be reproduced experimentally. In rabbits the experimentally produced immunity did not always prove permanent, fatal spreads and death sometimes ensuing, even after absorption of the miliary lesions; hence the factors of individual susceptibility and dosage and manner of original infection are considered important. Adult-type pulmonary tuberculosis is characterized by the isolation of the process in the lung. These experiments suggest that this feature is dependent upon the peculiar allergic condition of incomplete immunity, with the characteristic formation of confluent focal infiltrations, (*Frühininfiltrat*), especially in the apical or subapical regions. Intratracheal reinfection caused these to appear in one to three weeks; they were particularly marked when the primary infection was also intratracheal. They progressed to caseation when the bacilli were virulent, but soon disappeared when they were avirulent. Intratracheal infection of controls produced small pulmonary foci which disappeared if the bacilli were of an avirulent strain but developed into mild tuberculosis if virulent. However, we are not justified in concluding by analogy that similar lesions in man are necessarily the result of exogenous reinfection. They do suggest that early infiltrations in the human frequently develop as the result of coarse aspiration from old pulmonary foci which erupt into the bronchial tree. Under special allergic conditions, haematogenous metastases may give rise to large caseous infiltrations and these can also be reproduced in rabbits by intravenous reinfection. The apical, corticopleural and basal regions are especially involved. Intravenous reinfection with virulent bacilli following intratracheal infection caused an isolated pulmonary tuberculosis with enormous confluent caseous infiltrations, contrasting with the miliary symmetrical lesions in controls; following intravenous infection it resulted in marked localization of infiltrations in the corticopleural regions, in true infraclavicular foci ("circular infiltrations") and in liquefying foci and cavities, such as are seen in early adult-type pulmonary tuberculosis. On the other hand, the chronic cavitary pulmonary tuberculosis in rabbits occurring from a single intravenous infection with a bovine strain of low virulence is a generalized process different from the postprimary isolated lesions of adult man. These experiments are believed to support the theory that isolated pulmonary tuberculosis in the adult is due to an allergic diminished hypersensitiveness, limiting the pathological process and converting extensive haematogenous spreads into one or more large infiltrations. A number of photographic and roentgenographic reproductions accompany the paper.—*Experimental Studies on Early Pulmonary Tuberculosis of the Adult Type, W. Pagel, Brit. J. Tuberc., October, 1936, xxx, 204.*—(*A. P.*)

Experimental Bronchogenic and Haematogenous Reinfection.—Experience has shown that haematogenous transmission of tubercle bacilli is not unlikely. The same type of pulmonary foci is found in early bronchogenic phthisis as in chronic generalization. In the latter the haematogenous origin of pulmonary and extrapulmonary foci is not doubted, and by analogy the identical early lesion in bronchogenic phthisis has been regarded as haematogenous. Animal experiments were conducted to ascertain whether the early

pulmonary lesion could be initated by bronchogenic or by haematogenic infection. About 115 rabbits were primarily infected with BCG, human strains, heat killed tubercle bacilli and acid-fast saprophytes. In some animals minute foci and fine miliary spreads were noted 8 to 30 days after treatment. About 6 weeks after the last injection the remaining animals were reinfected intratracheally or intravenously with .001 to .01 mgm. of virulent bovine bacilli. This same dose killed all controls in 38 to 60 days by generalized miliary tuberculosis. In the rabbits sensitized with avirulent bacilli, virulent reinfection reproduced, in the main, features of the adult type of human tuberculosis in that the lesions were primarily pulmonary. The most consistent feature of the lesions in treated animals was limitation of the process to one organ and it seems independent of an immunizability varying with the individual animal. In 60 per cent of the animals the tuberculous process was protracted and in 5 cases avirulent infection conferred immunity to virulent reinfection. In 3 instances a miliary dissemination occurred but later disappeared. Large individual infiltrations occurred in 60 per cent of the cases. Intratracheal reinfection caused large infiltrations which may be regarded as counterparts of the infiltrations in man produced by course aspiration from previous recrudescent foci. Circular or square infiltrations and cavities typical of early pulmonary tuberculosis of human adults were obtained in subapical or corticopleural regions of the lung by means of intravenous reinfection. The results of the reinfection of allergic animals may be interpreted as partial immunization with suppressed hypersensitiveness, from which all intermediate stages to complete immunization were observed.—*The Reproduction of Early Pulmonary Tuberculosis of the Adult Type by Bronchogenic and Hematogenous Reinfection, W. Pagel, J. State Med., February, 1937, xlv, 63.*—(*L. F. B.*)

Human Inoculation with Bovine Tubercle Bacilli.—By culturing tissues from biopsies of tuberculous cutaneous lesions and organs of laboratory animals inoculated with these biopsies it has been possible to make biological studies of these bacilli having their origin in these lesions. The majority of these organisms were tubercle bacilli of the human type, some were bovine strains and an exceptional one was an avian strain. Experimentation with these microörganisms shows that their virulence becomes attenuated, probably because of the conditions under which they develop. An old bovine strain of tubercle bacilli which had become almost avirulent for the rabbit became accidently the incitant of a skin lesion on the thumb of one of the authors. The lesion was studied histologically and culturally. The histological examination revealed supporting evidence of the atypical character of so many tuberculous skin lesions. Cultures on Loewenstein's medium yielded smooth, round, white colonies which when reseeded on potato medium became dry and lightly pigmented. These colonies had the same general appearance as the original strain. The two strains were identical on Sauton's medium. Guinea pigs and rabbits inoculated in various ways with the organism isolated from the skin lesion all succumbed to the infection with generalized tuberculosis. The organism thus behaved in the characteristic manner of a true bovine strain of tubercle bacilli. Thus it is shown that a strain of bovine tubercle bacilli which had become attenuated showed a normal virulence for laboratory animals after a period of incubation of two months in the human skin in contrast to most tubercle bacilli isolated from skin lesions which usually have a low virulence for experimental animals.—*Autoinoculation intradermique d'une souche de laboratoire de tuberculose bovine; modification consécutive de la virulence, J. Bablet, M. Ducourtrioux & F. Bloch, Compt. Rend. Soc. Biol., December 12, 1936, cxxiii, 1086.*—(*M. T. W.*)

Effect of Fatty-Acid Compounds on Experimental Tuberculosis.—Since ethyl stearate has been known to retard the development of tuberculous lesions in experimental animals, ethyl palmitate and laurate were used to determine their effects upon tuberculous lesions. Guinea pigs were inoculated with virulent strains of tubercle bacilli, bovine or human types, and treated with 0.5 cc. of ethyl stearate, palmitate or laurate. At autopsy six to seven weeks later the lesions in the treated animals had not progressed with the same degree of rapidity as had the lesions in the control guinea pigs not treated, which all showed generalized tuberculosis. The glandular involvement in all the treated animals was markedly less. In some of the treated animals the spleens were entirely free of tuberculous lesions.—*Action retardante exercée par des injections sous-coutanées de stéarate, de palmitate ou de laurate d'éthyle sur l'évolution de la tuberculose expérimentale du cobaye, L. Nègre, A. Berthelot & J. Bretey, Compt. Rend. Soc. Biol., November 28, 1936, cxxiii, 864.*—(*M. T. W.*)

Elimination of Tubercle Bacilli by Way of Intestinal Tract.—Chickens which showed themselves totally refractory to massive doses of bovine tubercle bacilli were reinoculated intravenously with bovine tubercle bacilli of the dysgonic S-variety. At intervals varying from twenty-four hours to seventy-five days following the inoculation, the faeces of the chickens were examined for the presence of acid-fast bacilli. The faeces were examined culturally and were inoculated into guinea pigs, rabbits and chickens. From one culture tube acid-fast bacilli, forming smooth white colonies, were recovered which, when inoculated into rabbits and guinea pigs, produced a generalized tuberculous infection. The bacilli failed to infect chickens. One guinea pig inoculated with faeces from a chicken inoculated twenty-four days previously with the dysgonic tubercle bacilli showed a clearly positive reaction to tuberculin thirty days after inoculation. The animal showed no gross lesions at autopsy at that time. Cultures of the organs yielded colonies of acid-fast bacilli which proved virulent to other guinea pigs and showed positive serological reactions to a specific bovine bacillus antigen. These experiments show that while the elimination of tubercle bacilli by the intestinal tract is slight and intermittent, nevertheless it does occur.—*Étude expérimentale de l'élimination, par voie intestinale, du bacille tuberculeux, C. Ajo, Compt. Rend. Soc. Biol., February 20, 1937, cxxiv, 614.*—(*M. T. W.*)

Absorption of Tubercle Bacilli through Digestive Mucosa.—Experiments were performed to determine the distribution of tubercle bacilli throughout the digestive tract when administered *per os*. Ten guinea pigs were given by mouth a bovine strain of tubercle bacilli of not very great virulence. Four animals were sacrificed one, four, eight and twelve days later. Duodenal washings and mucosa were examined by cultural method and by animal inoculation for the presence of tubercle bacilli. By the end of the eighth day following the infection no tubercle bacilli could be found in the duodenal mucosa or in the washings. The guinea pigs which were permitted to live became positive to tuberculin. Sacrificed four months later they showed a very discrete type of tuberculosis. The walls of the digestive tract showed no visible tuberculous changes. In a second experiment a more virulent strain of tubercle bacilli was administered in the same way to sixteen guinea pigs. Four animals were sacrificed ten, twenty, thirty and forty days later. In these guinea pigs no tubercle bacilli could be demonstrated in the duodenal mucosa. The animals became positive to tuberculin after the twentieth day following the infection. The remaining animals were sacrificed three to four months later. They showed marked generalized tuberculosis at autopsy. The duodenal mucosa remained uninfected. These experiments tend to show that whatever the degree of virulence of the tubercle bacilli when given *per os* the organisms do not remain in the duodenum after the tenth day following the infecting meal. The absorption of the bacilli by the digestive mucosa, their diffusion and their development of the infection is in direct relation to the virulence of the strain used.—*La dispersion du bacille de Koch administré per os et la diffusion de l'infection tuberculose d'origine digestive, F. Pezzangora, Compt. Rend. Soc. Biol., October 24, 1936, cxxiii, 476.*—(*M. T. W.*)

Elimination of Tubercle Bacilli in Rabbits and Guinea Pigs.—The routes of elimination of tubercle bacilli have been studied by various investigators and with a diversity of opinion among them. Because of these contradictory reports, studies were made on the elimination of bacilli by means of the biliary and tracheal routes. Guinea pigs and rabbits received intravenous or intracutaneous inoculations of different strains of tubercle bacilli, human, bovine and avian types, paratubercle bacilli and strains isolated from guinea pigs. In order to eliminate any contamination of the tracheal and biliary tracts by bacilliferous blood, all animals were bled first. The blood and urine were cultured. Out of thirty-nine infected guinea pigs twenty-one showed a weak elimination of bacilli through the bile, five of which cases were positive only on animal inoculation and negative on culture. Elimination of bacilli by the tracheal route was less frequently observed. Seven animals only out of the thirty-nine harbored tubercle bacilli in the trachea. The results of the blood cultures were irregular. A study of bacillaemia shows that there does not exist any relation between the virulence of the strain and the number of bacilli found in the blood. Tubercle bacilli were found in the urine of only one animal out of twenty-seven examined. In experimental tuberculous rabbits, elimination of tubercle bacilli was found to be by tracheal route more often than by the biliary route. Twelve animals out of twenty eliminated bacilli through the trachea. Five out of eleven animals showed positive biliary findings. Thus it is shown that tubercle bacilli are eliminated more regularly by the

tracheal route in the rabbit and by the biliary route in the guinea pig. The elimination commences shortly after the infecting inoculation.—*Elimination précoce des bacilles tuberculeux par des voies diverses chez le lapin et le cobaye, R. K. Goyal, Compt. Rend. Soc. Biol., October 17, 1936, cxxiii, 379.*—(*M. T. W.*)

Concurrent Brucella and Tuberculous Infections in Guinea Pigs.—Since brucella and tuberculous infections so frequently occur in cattle simultaneously a series of studies was undertaken to determine which of the infections was capable of influencing the other. It has already been shown that a single inoculation of heat killed bacilli of Bang superimposed upon an existent infection of Koch's bacilli in guinea pigs did not change the course of the tuberculous infection while three successive inoculations of the heat killed bacilli did markedly affect the tuberculosis. A brucella infection superimposed upon a tuberculous bacillaemia renders the tubercle bacilli more readily demonstrable in the blood-stream. Two groups of experiments using living Bang's bacilli were performed in the effort to show the exact effect of a brucella infection upon tuberculosis. Guinea pigs with tuberculous infections of human and bovine origin of varying duration were inoculated with Bang's bacilli. The conclusion was that in general the superimposed brucella infection appeared to have an unfavorable although slight influence upon tuberculized guinea pigs. In the second series of experiments tuberculous infections were superimposed upon existing brucella infections. The animals rapidly became emaciated and died. The tuberculous involvement could scarcely be detected at autopsy. This second combination proved particularly deleterious to the guinea pig.—*Evolution expérimentale des infections tuberculeuse et brucellique, associées chez le cobaye, W. Sarnowieg, Compt. Rend. Soc. Biol., October 24, 1936, cxxiii, 452.*—(*M. T. W.*)

Response to Avirulent Tubercle Bacilli.—The question whether exudation, with polymorphonuclear predominance, or proliferation of the tissue, with histiocytic superiority, has priority in the formation of the tubercle is still unsettled. Also, the remote response of the tissues such as the reticuloendothelial system, where tubercle bacilli are not demonstrable by ordinary methods, has been neglected. The present article is a study of this remote response when an avirulent organism (BCG), which tends to remain localized, is injected. Also, of the question do tubercles in various organs develop similarly. An attempt is made to correlate the humoral and tissue responses. Guinea pigs were inoculated intracardially with from 10 to 15 mgm. of BCG and killed at intervals of ten minutes, one, three, five, eight, sixteen, twenty-four, thirty and forty-eight hours, three, five, seven, nine and fifteen days and one, two, three and fourteen months. Histological examinations of the lungs, lymph nodes, liver, spleen, kidneys and heart were made. Also blood counts were done at frequent intervals. Results of the microscopic studies are given in detail with accompanying illustrations. In the lungs the bacilli were first ingested by the polymorphonuclears and only after seventy-two hours or more was there a histiocytic predominance. Swelling of the septal cells in areas where there was no localization of the bacilli began almost at once after the injection of the bacilli and was well pronounced by the third hour. This process remained active during the formation of the tubercle and was evident after the tubercle subsided. In the liver the early leucocytic response was infrequent, the Kupffer cells or histiocytes forming the nodules. In fact the swelling of the Kupffer cells as well as the perivascular histiocytes was more prominent than the formation of tubercles. The reticuloendothelial system of the kidney and spleen also responded rapidly even in the absence of noticeable bacilli. Very shortly after the intracardiac injection the total number of white cells was increased. The granulocytes benefited almost entirely from this elevation. After twenty-four hours their number fell gradually to normal. The monocytes did not begin to rise appreciably until the third day, were usually at the peak from the seventh to the fifteenth day, and then receded. The increase in the number of leucocytes in the blood was transmitted and seen in the tissues. Although swelling and proliferation of the histiocytic cells began almost immediately, the number of monocytes in the blood did not increase appreciably during this early response of the reticuloendothelial system. The monocytes lagged behind the appearance of the histiocytic elements in the tuberculous nodules. Only when the tubercle was fully formed was the number of monocytes appreciably increased in the blood. If bacilli are first engulfed by granulocytes, as occurs within the blood, their presence in the tissues attracts by chemotactic action other granulocytes, whereas if organisms are first phagocytosed by focal histiocytes such foci

call forth a local histiocytic response. The number of bacteria also plays a rôle; large numbers are associated with granulocytes and small numbers with histiocytes. What is the mechanism responsible for the generalized response of the reticuloendothelial system? The author favors the view, based on some previous studies, that this is a result of a general diffusion of submicroscopic forms. Although tubercles formed by avirulent and virulent tubercle bacilli are similar, the former (BCG) does not cause severe damage to the tissue that leads to necrosis or caseation and the tubercle formed regresses completely, usually without fibrosis or calcification.—*Focal and General Tissue Responses to an Avirulent Tubercle Bacillus (BCG), S. R. Rosenthal, Arch. Path., September, 1936, xxii, 348.*—*(J. S. W.)*

Effects of Gonadotropic Hormones on Tuberculosis.—It has long been known that pregnancy may benefit pulmonary tuberculosis provided the disease is not too advanced or active and progressive. There is at first an apparent improvement which disappears in later pregnancy. It is now known that there is an increased secretion of estrogenic and gonadotropic hormones during pregnancy, especially in the earlier stages. In fact, the presence of the gonadotropic hormone in the urine is used as a pregnancy test (Ascheim-Zondek). Experiments were done to determine the effect of the gonadotropic hormone in animal tuberculosis with the idea that the hormone might be a factor in the resistance displayed by pregnant women. Rabbits and guinea pigs were infected with virulent bovine tubercle bacilli and treated with several of the following: antuitrin-S, follutein, anterior pituitary extract, pregnant mare serum and emmenin. In reporting the degree of the infection the results were graded from 0 to 4+, depending on the severity of the disease present. In the first experiment 24 young female rabbits were divided into four groups and three of the groups were pretreated for 10 days with antuitrin-S, follutein and anterior pituitary extract respectively. All animals then received tubercle bacilli and hormone treatment was continued daily until the animals were autopsied, at 74 to 114 days after infection. In general, when an animal died in one group, an animal from each of the other groups was killed for comparative study. The average degree of tuberculous involvement of the various groups is reported as: antuitrin-S 1.3+, follutein 2+, anterior pituitary extract 3.8+ and controls 3.7+. In another experiment the same three hormones were tested on male guinea pigs, but there was no pretreatment. The daily hormone treatment was begun on the day of infection. The animals were sacrificed in groups of 4 at 35, 36, 37, 38 and 41 days after infection. The average involvement for this experiment was: antuitrin-S 1.2+, follutein 3.2+, anterior pituitary extract 4+ and controls 3.8+. Another group of guinea pigs was treated the same way, but received a smaller infecting dose of tubercle bacilli. The follutein was omitted. In this series the average involvement was: antuitrin-S 1.8+, anterior pituitary extract 3.3+ and control 3.8+. In an attempt to determine whether temporary hormone treatment would influence survival time a third group of guinea pigs was infected and treated in exactly similar fashion. Treatment was discontinued at 41 days after infection and the animals survived 149 to 305 days. It was found that hormone treatment did not lengthen survival time. A group of female guinea pigs was injected with the bovine bacilli and subgroups received antuitrin-S, pregnant mare serum, normal mare serum and emmenin. The pregnant mare serum was used because it contains all the hormones of pregnancy; the hormone emmenin because it is characteristic of pregnancy and is effective when given by mouth by which route it was administered in the experiment. One animal in each subgroup was killed as in the first experiments. The average degree of involvement was: antuitrin-S 1.7+, pregnant mare serum 1.9+, normal mare serum 3+, emmenin 3.7+ and no hormone (control) 3.4+. The results from these experiments suggest that the gonadotropic principle which appears during pregnancy may be an important factor in the increased resistance displayed by the pregnant tuberculous woman. The breakdown of this resistance that occurs during the after stages of pregnancy may perhaps be correlated with the diminution of this hormone, which begins after about the fifth or sixth month and ends with the entire disappearance of the hormone a few days after delivery. The mechanism whereby the gonadotropic hormone influences tuberculosis has not been determined.—*The Effects of Gonadotropic Hormones in the Treatment of Experimental Tuberculosis, M. M. Steinbach & S. J. Klein, J. Exper. Med., February, 1937, lxvi, 205.*—*(J. S. W.)*

Lesions Produced by Silica and Tubercle Bacillus.—In human cases, where tuberculosis and silicosis are associated, it is often impossible to be certain of the aetiology of a particular lesion, since the

lesions of the two diseases are essentially similar. A proper diagnosis is made only on reviewing the gross appearance of the entire lung and on the examination of a number of histological sections. The lesions of experimental silicosis in animals resemble even more closely those of tuberculosis. One reason for this is the similarity in the tissue response to silica and to the tubercle bacillus. Silica can cause every type of cellular response found in tuberculosis. The reaction to the tubercle bacillus is more uniform because its constitution is more or less constant and it soon establishes a limited equilibrium with the tissues of the host. The reaction to silica is largely determined by the number and the size of the particles that come to rest within a given focus in the body. Both irritants cause varying degrees of proliferation, exudation and necrosis, resulting in a nodular type of foci. It would seem that both irritants are relatively insoluble, but that perhaps both of them continually liberate minute amounts of irritating substances. Both irritants react on the mononuclear phagocyte to alter its internal structure in a similar manner. If the lipoid elements of the tubercle bacillus are responsible for the production of epithelioid cells, it is difficult to imagine what comparable substance could be liberated from the molecule of silicon dioxide to produce very similar cells. Both irritants injure mononuclear phagocytes so that multinuclear giant cells are produced. Mechanical stimulation alone does not produce Langhans' giant cells, and silica produces them only when the particles are large enough to exert some mechanical effect and at the same time small enough to present a sufficient amount of active surface in contact with the cytoplasm of the phagocytes for chemical reaction to occur. It is of interest to note that this optimum size approximates that of the tubercle bacillus and measures from 0.1 to 4 micra in diameter. The nodular character of the lesions in both silicosis and tuberculosis is also probably dependent on altered behavior of the mononuclear phagocyte. In each case this cell is responsible for the concentration and the walling off of the irritant in a localized focus. The surfaces of the irritated cells seem to become viscous so that they adhere to one another. As they proliferate about a collection of particles or bacilli in the tissues they tend to remain *in situ* and form the primary nodule. The subsequent proliferation of fibroblasts contributes collagenous fibres that bind the other elements into a compact mass. The mature fibrosis of silicosis is somewhat different from that caused either by the tubercle bacillus or by the other irritants. Intercellular fibres begin to increase in number and size early in the course of the reaction. They resist the necrotizing action of the silica unless its concentration is excessive. These fibres stain strongly with acid dyes such as eosin. If one accepts the solution hypothesis, it is quite possible that the dissolved silica forms a physical or chemical combination with the collagenous fibres which prevents its diffusion beyond the limits of the nodule. This would explain the lack of reaction in surrounding tissues and in remote excretory organs. Not all silicotic nodules undergo these changes for the characteristics of the reaction are determined by the local concentration and the size of the particles. A small number of coarse particles produces proliferation with little or no necrosis. Moderate concentration of fine particles is responsible for fibrous nodules with necrotic centres. With excessive numbers of minute particles proliferation is overshadowed by degeneration and necrosis. On the other hand, the primary response to the tubercle bacillus is more uniform and the number of organisms that will develop in a primary tubercle after inhalation infection never exceeds a certain maximum. Whenever bacillary multiplication becomes excessive, the lesion spreads to new areas. Silicotic lesions are also progressive, but added reaction occurs in the immediate vicinity of the original site of localization. Particles that once become surrounded by a zone of fibrosis are not carried elsewhere unless this fibrous tissue is destroyed by inflammatory changes usually due to secondary bacterial infection. The presence of tubercles composed of epithelioid cells, but produced by silica, does not create hypersensitiveness to tuberculin.—*The Similarity of the Lesions Produced by Silica and by the Tubercle Bacillus, L. U. Gardner, Am. J. Path., January, 1937, xiii, 13.*—(*J. S. W.*)

Phosphatide Acid and Production of Tuberculous Granulomata.—The present work deals with a study of the phosphatide and neutral fat of the tubercle bacillus. The A-3 phosphatide of Anderson contained 2.3 per cent phosphorus and 0.4 per cent nitrogen and two new fluid saturated fatty acids, tuberculostearic acid and the optically active d-phthion acid. As water soluble split products there was, besides glycerinphosphoric acid and ammonia, about 30 per cent carbohydrate. It was shown that the nitrogen content of the phosphatide obtained by Anderson's method was due to contamination with ammonia salts which had been adsorbed from the synthetic

nutrient fluid. This made it obvious that it was not a question of any of the known lipoids such as lecithin, kephalin, or sphingomyelin. After treating the crude phosphatide with water the nitrogen can be separated off as ammonium salts and the carbohydrate is partially removed at the same time. It is difficult to decide whether the carbohydrate which remains with the phosphatide is only adsorbed on the latter and thereby represents an impurity. The waxy constituents which are free from both nitrogen and phosphorus do not give sterol reactions. Their chief split products are unsaponifiable waxes and can be separated from the phosphorus containing lipoid only with the greatest of difficulty. This is largely due to their similar solubilities. Pure phosphatide acid is isolated as follows: with dilute acid the organically bound magnesium is split off, the remaining free acid is transformed into a lead salt and, after splitting off the lead, there remains a phosphatide acid which contains 3.8 per cent phosphorus, and is free of nitrogen and carbohydrate. That the phosphatide acid is a diglyceride phosphoric acid is indicated by the abscence of nitrogen and the fact that it behaves as a dibasic acid when titrated with alkali. It is similar to the diglyceridephosphoric acid isolated by Chibnall and Channon from plant cytoplasm, but with the distinction that the phosphatide from the tubercle bacillus contains an optically active fatty acid of high molecular weight, hitherto unknown in any other situation in nature. Sabin and her coworkers found that the tissue changes produced by phosphatide from tubercle bacilli far surpassed in intensity and in specificity those produced by the fat or wax, and only with very great and repeated doses could tuberculous granulomata be produced by the latter. In the present studies the material used for intracutaneous inoculation was dissolved in vaselin oil, 10 mgm. per cc. The test dose was 0.1 cc. or the equivalent of 1 mgm. of the pure phosphatide acid. All material used had a phosphorus content of 3.4 to 3.8 per cent. None of it contained nitrogen. Tubercle-like granulomata appeared from the fourteenth day through the third week following inoculation, while A-3 phosphatide was able to cause such developments only after a month had elapsed. Phosphatide acid from bovine tubercle bacilli produced in rabbits a more violent and more persistent skin reaction than that from human strains. This was confirmed by microscopical sections. The reverse was the case in tests made on humans. Tests made on humans with material from human strains were biopsied after six weeks. There was a marked change in the cutis with many typical tubercles with giant cells. There was marked fibrosis, and giant cells could be seen lying in dense fibrous tissue. Phosphatides make up not more than 2 per cent of the body of the tubercle bacillus. One mgm. of this would correspond to a dose of tubercle bacilli which is scarcely ever realized in a tubercle as a localized mass. Nevertheless this dosage is much less than that required of any other fraction of the microörganism to produce similar results. Control experiments with other lipoids, lecithin from eggs, kephalin and sphingomyelin from brain, never called forth similar reactions. It is conceivable that the specific activity of the phosphatide acid lies in its chemical constitution as a whole. Against this view is the fact that the phosphatide acids from plants do not act this way. The other possibility is that the specific action lies in one of the two previously unknown fatty acids which Anderson isolated from the A-3 phosphatide. These are both foreign to the animal organism and it is likely that one of them might call forth the specific response. Sabin and her coworkers were able to produce tuberculous granulomata with the optically active d-phthion acid obtained as a split product of the phosphatide. The intensity of the tissue response was considerably less than that evoked by the phosphatide itself, however. Pure phthion acid was not available for the present work. A fatty acid mixture obtained by hydrolysis from A-3 phosphatide was studied. The tissue reaction to this material was marked by an active inflammatory response with abscess formation. By using poultices the reaction could be followed into a chronic stage which resembled the phosphatide acid reaction. After four weeks there could be observed at the edge of the abscess, foci containing giant cells and lymphocytic infiltration. Leucocytes were still present in the abscess wall. The powers of other fatty acids to invoke tissue responses were also studied. These included oleic, linoleic, linolinic, ricinoleic, erucic and chaulmoogric acids. They were chosen in order to observe the influence of chain length, degree of saturation and the presence of the ring structure. These called forth only nonspecific reactions which were in many instances violent, but at times quite insignificant. It is therefore likely that the fatty acids of the phosphatide-acid molecule have a special action. So far the optically active d-phthion acid has been isolated by Anderson only from human

strains of tubercle bacilli. Chargoff has found the corresponding fraction from bovine and avian bacilli and from saprophytic acid-fast microörganisms to be optically inactive as well as biologically inactive. It is likely, however, that the lipoids of these bacilli do contain a d-phthion acid which is very difficult to demonstrate. In the present investigation it has been shown that the phosphatide from bovine strains could produce in rabbits a stronger reaction than material from human strains. This certainly speaks for the presence of an active fatty acid constituent in the bovine phosphatide. Phosphatide acid has rather special solubility characteristics. It is soluble in oils and fats like other lipoids. On the other hand like every hydrophilic colloid it can be easily emulsified in water to form a stable emulsion. This peculiarity which it has in common with lecithin lies in its chemical structure. The molecule contains two polar groups, a hydrophobic paraffin ring responsible for its solubility in fats, and a hydrophilic glycerophosphoric acid to which it owes its ability to form emulsions. These peculiarities are largely responsible for the rapidity with which phosphatide acid can be taken up by the cells. Once taken into the cell it presumably undergoes a hydrolytic breaking down whereby free fatty acids are liberated, among them d-phthion acid. The latter can then in its finely dispersed condition unfold its specific irritating qualities which eventually lead to the formation of the tuberculous granuloma. Attention should be called to the fact that phosphatide acid sets up in sick (allergic) animals no more violent reactions than in the normal healthy animal. It is especially to be noted that there are no differences in the early exudative phase of the inflammatory process. Hitherto specificity of chemical type has been demonstrable only by serological reactions. The above work with material from bovine and human strains of the tubercle bacillus demonstrates such chemical specificity by the tissue response.—*Beitrage zur Spezifität der Entzündung mit besonderer Berücksichtigung des tuberkulösen Granuloms, F. Roulet & K. Bloch, Virchow's Arch., December 23, 1936, ccxcviii, 311.*—(*C. L. D.*)

Reinfection with Virulent Tubercle Bacilli in Guinea Pigs Treated with S Variant.—When guinea pigs are infected with S variants of bovine tubercle bacilli subcutaneous reinfections with R strains remain localized at the site of introduction or in the draining lymph nodes. A series of experiments was made in the attempt to show what becomes of the bacilli of reinfection when administered intravenously. Guinea pigs were given intracutaneous immunizing doses of an S variant of a highly pathogenic strain of bovine tubercle bacilli. The animals were reinfected intravenously twenty-five, thirty or seventy days later with a virulent R strain of human tubercle bacilli. The guinea pigs were sacrificed at varying intervals from two to fifty-six days after reinfection. Their lungs, spleen, liver and certain lymph nodes were cultured on Loewenstein's medium. The number of resultant R and S colonies showed whether the bacilli of reinfection were eliminated or destroyed in the tissues. The results showed that in the guinea pig the resistance conferred by an immunizing infection manifests itself largely in the spleen, liver and lungs. This is accomplished not so much by a bacteriolytic process as by an immobilization of the bacilli in the foci which they cause.—*Sort des bacilles d'épreuve dans l'organisme des cobayes tuberculeux, surinfections par voie veineuse, A. Boquet & R. Laporte, Compt. Rend. Soc. Biol., April 17, 1937, cxxiv, 1156.*—(*M. T. W.*)

Blood Sedimentation and Antibody Response in Rabbits Inoculated with S and R Strains of Tubercle Bacilli.—Preliminary inoculations of S variants of tubercle bacilli confer a certain degree of immunity to guinea pigs and rabbits to subsequent inoculations of virulent R strains. In view of these findings it seemed interesting to study the production of tuberculosis antibodies and the sedimentation of red blood corpuscles after inoculations of S strains of tubercle bacilli and in the period of experimental infection with R strains. The antibody response was exactly the same in the rabbits which received the avirulent bacilli. They were given varying intravenous doses at varying intervals up to and including eight days apart. The antibody response began about the second or third day, increased to the twentieth day, then diminished rapidly. In animals receiving inoculations at long intervals the tuberculosis antibodies appeared after a delayed period and were of a low titre. The sedimentation of the red blood cells remained normal in all of the animals which were inoculated with the S variant. Rabbits which had already received inoculations of the avirulent S strain were reinoculated with a virulent R bovine strain. Control animals inoculated only with the R bovine bacilli were observed side by side with the former animals. In

the former series of animals the antibody response rose and diminished while with the control animals the titre of the antibodies remained at the same level from the onset of the disease until the death of the animals. In the preinoculated animals the blood sedimentation remained normal while in the control rabbits the sedimentation of the red blood corpuscles was markedly increased. —*Les anticorps tuberculeux et la vitesse de sédimentation globulaire chez les lapins prémunis par injection intraveineuse de bacilles tuberculeux a colonies lisses, puis éprouves avec un bacille tuberculeux virulent, F. Dwelshauvers, Compt. Rend. Soc. Biol., November 7, 1936, cxxiii, 549.*—(*M. T. W.*)

Lesions Produced by Dissociated Tubercle Bacilli.—Dissociation of a strain of tubercle bacillus was accomplished in 1927 and since then the process has been applied to nearly all types including the well-known laboratory strains. In general, there are two types of dissociation—the forced and the spontaneous. Forced dissociation is produced by manipulation of subculturing procedure and environment. It is the positive method and accounts for most of the published reports on the subject. Spontaneous dissociation is a change which occurs in a strain of known qualities. It usually involves only the characteristic of virulence and this change is in the direction of avirulence. A familiar example is the R1 strain whose history is well known. BCG has resulted from a combination of methods. It has now become a pure-line avirulent strain. The characteristics which forced dissociation has been found to affect are: colony form, virulence, bacillary morphology, chromogenicity, immunological properties and chemical composition. The nomenclature of variants is obscure and confusing. The terms "R" and "S" have been taken to mean rough and smooth (colonies), as well as resistant and sensitive to environment. Since single strains of bacilli have yielded more than two variants, and since there is no invariable correlation between colony forms and certain levels of virulence, the authors have adopted the following terminology: The colonies of a strain are described as R (rough) or S (smooth), with the modifying term "ch" to denote chromogenicity (if present). Subscriptions are added to each to indicate the variant as being virulent (v), or avirulent (a) or intermediate (in). Thus we have H37, R_a and R_v variants, etc. The object of this report is to describe the pathological picture produced by variants derived from two well known strains of tubercle bacilli, an avian strain and H37 (human). Each had a relatively high virulence at the time of dissociation. Guinea pigs, rabbits and chickens were inoculated with various kinds and quantities of the variants and the pathogenesis of the disease studied. Results are given in considerable detail. The following points seem important. The progress of infection depends on the formula $R = V \times \#$ (resistance = virulence $\times$ numbers of bacilli). In the present series virulence was found to be the most important single factor. Relative virulence dictated the mortality figures. The amount of gross and microscopic disease was directly proportionate to the virulence. The avirulent variants produced so little disease as to be invisible to gross inspection. The numbers of bacilli found in direct smear and in section were also proportionate to virulence. They reflected the parasitic ability of organisms. The relationship between virulence and colony morphology persisted through the animal passage. When other factors (portal of entry, etc.) were equal, the number of bacilli injected affected proportionately the duration, amount and type of disease, and the number of bacilli in the tissues. The portal through which the bacilli enter directly influences the immediate and end-results of primary infection. It determines the localization of bacilli, the rapidity of spread, the availability of vital organs, the site of lesions and the later spread. The portal, therefore, modifies the effects of virulence. The lesions caused by the virulent variants tended to be large, rapidly growing, spreading and to show evidences of acute inflammation and allergy. The mononuclear type of cells were mature and epithelioid. The lesions formed by the avirulent variants tended to be small, to grow slowly and to regress daily. Immature monocytes were the chief constituents of the tubercle. Variants of intermediate virulence produced intermediate lesions. The fundamental tissue reaction to different types of tubercle bacilli were found to be the same. The cells taking part in the formation of the tubercle are the polymorphonuclear neutrophilic leucocyte, the mononuclear leucocyte and the lymphocyte, usually in the order named. The most important of these, the mononuclear cell either comes from the blood (monocyte) or is of regional origin (clasmatocyte). Cells from both origins are present soon after infection, the more available source producing the greater supply. The epithelioid cell, the mature (sick) monocyte, is said to be produced by bacillary phosphatide. The avirulent variants reproduce slightly and stimulate maturation only slightly; the virulent

variants multiply, are destroyed in larger numbers, and cause greater stimulation. The presence of a specific phosphatide content in a variant is unsettled. The function of the lymphocyte is not surely known. It seems to be associated with regressive lesions and with resistance of the host. The blood pictures which resulted from infection with the different variants were, in general, reflections of the pathological conditions which have been described. The types of responses and their intensities were especially dependent on virulence. The relative number of tubercle bacilli in the lesions caused by the different variants was the most positive expression of virulence. Other conditions being equal it was in direct proportion to the amount, the progressiveness, the septic tendency and the fatality of the disease. The virulence of the variants was found to be closely related to the colony morphology of their cultures. Virulence seemed to be more important than the other factors which are known to influence pathogenesis in experimental tuberculosis. So far as is known it is not related to differing bacillary composition.—*The Pathogenesis and Fate of Tubercle Produced by Dissociated Variants of Tubercle Bacilli, W. H. Oatway, Jr., & W. Steenken, Jr., J. Infec. Dis., November–December, 1936, lix, 306.—(J. S. W.)*

Bacillaemia in Pulmonary Tuberculosis.—In the present study an attempt was made to answer several questions. Will the media used support the growth of small numbers of tubercle bacilli? Are the techniques employed efficient in concentrating the microörganisms if they are present in the blood, and does the technique decrease the viability of the bacilli? Selecting confirmed cases of progressive pulmonary tuberculosis, can the presence of the tubercle bacillus be demonstrated in the circulating blood? The results obtained showed that the media employed (Loewenstein's) were adequate to support the growth of the bacillus. The revised technique of Loewenstein (employing water to lyze the blood) efficiently recovers the microörganisms. The sulphuric-acid treatment does not inhibit the growth of the tubercle bacillus. In 31 cases observed, none showed macroscopical evidence of growth, and two, or 6.5 per cent, showed some microscopical evidence of acid-fast particles which were not capable of producing growth on fresh media. It would seem therefore that bacillaemia is not present in pulmonary tuberculosis, or that it may be present for a very short time, and then sporadically following the breakdown of a tubercle into the blood-stream. This makes the detection of the tubercle bacillus problematical, or that the bacilli may be present in such few numbers that they escape detection. It is impractical and undesirable to take large amounts of blood from a patient to increase the numerical chance of demonstrating the bacillaemia. It is believed, however, that if a single viable bacillus be implanted on this medium it will grow. No positive evidence was presented indicating the presence of a tuberculous bacillaemia; if there is a bacillaemia, it occurs only rarely and sporadically.—*Bacillemia in Pulmonary Tuberculosis, R. C. Rosenberger & L. Merves, J. Lab. & Clin. Med., January, 1937, xxii, 4, 358.—(F. G. P.)*

Differentiation of Tubercle Bacilli.—Since the acid-fastness of tubercle bacilli may vary, resulting in the decolorization of some organisms when strong acids are used, the author studied other means of differentiation. Dold found that a mixture of 40 per cent urea with absolute alcohol in the proportion of 1 to 9 differentiated the gram-positive bacteria. The author compared this method with the Ziehl-Neelsen method, using hydrochloric acid alcohol as the decolorizing agent. He found that the urea-alcohol mixture decolorized all bacteria, except the tubercle bacillus, and in addition showed an unstained capsule about the organism. The ability of other chemical substances to differentiate the acid-fast bacteria was also studied. It was found that the urea derivatives guanidin nitrite and guanidin rhodanate in 50 per cent concentration mixed with alcohol in a proportion of 1 to 9 gave good differentiation. Good decolorization was also obtained with 7 per cent sodium chloride, 10 per cent ammonium sulphate, 7 per cent ammonium chloride and 10 per cent potassium acetate, when mixed in the proportions of 1 to 9 with ethyl alcohol. The degree of decolorization obtained with these chemicals greatly exceeded that obtained with the ethyl alcohol alone. With the exception of ammonium chloride watery solutions of the chemicals had no decolorizing effect. Decolorization is not due to osmotic factors, since solutions of dextrose in alcohol do not decolorize. As to the effectiveness of the various alcohols, it was found that butyl and amyl alcohol had no decolorizing action and were not miscible with water. Methyl and propyl alcohol have slight decolorizing action. Ten per cent solutions of sodium chloride, sodium acetate, potassium acetate, potassium carbonate and 5 per cent solution of potassium cyanide in methyl alcohol decolorized all

bacteria except the tubercle bacillus. Similar results were obtained with 10 per cent solutions of sodium acetate, potassium acetate, potassium carbonate and 40 per cent solutions of urea in propyl alcohol. Preparations decolorized with methyl or propyl alcoholic solutions of the above named chemicals show the tubercle bacilli to be dark red in color. Results similar to the above were obtained when ten per cent solutions of potassium acetate, potassium citrate and 40 per cent solutions of urea in glycol were used.—*Über neue Entfärbungsmittel für die Tuberkelbazillenfärbung, C. Eberspacher, Zentralbl. f. Bakt., December, 1936, cxxxviii, 92.*—(*J. D. A.*)

Organ Extracts as Culture Media for Tubercle Bacilli.—Extracts were made of kidney, liver and lung of guinea pigs and rabbits to be used as culture media for tubercle bacilli. These extracts were added in 10 cc. amounts to 15 cc. of glycerine broth and tested for a possible inhibitory action on the development of tubercle bacilli. A very small inoculum of bacilli was added to these media and examined at the end of twenty days. The extract of the kidney of the guinea pig had prevented the multiplication of the bacilli and had killed the seeded organisms. The liver extract of the guinea pig and the rabbit permitted only a weak development of bacilli, which did not grow on reseeding. The extract of the spleen permitted a weak growth. Extracts from the lung of both animals permitted the culture to grow more luxuriously than any other extracts or the control medium. A heavier inoculum was made into the media and the growth examined in thirty-five days. In the media containing extracts of kidney and lung only a rare bacillus could be found. In the extract of spleen the bacilli grew abundantly, as they did in the control broth. The liver-extract broth permitted a moderately heavy growth. A third series of cultures was made by making a heavy seeding of organisms. These cultures were examined two months later. The kidney-extract broth supported a good growth, but changed the morphology of the bacilli to long bacilli with swollen ends. Spleen-extract medium supported a weak development. The lung-extract broth permitted a heavy growth, but produced a morphological change in the bacilli to very short rods. The liver-extract prohibited the growth in this series.—*Influence de divers extraits d'organes sur les cultures liquides homogènes du bacille tuberculeux, F. Arlong, L. Thevenot & J. Viallier, Compt. Rend. Soc. Biol., December 21, 1936, cxxiv, 164.*—(*M. T. W.*)

Tubercle Bacilli in Milk by Culture.—Forty-five positive cases were obtained in 10 to 14 days from 904 samples of milk from single cows all of which had been negative on microscopic examination. The positive cases were confirmed by positive postmortem examination of the animal concerned. The milk deposit, after centrifuging, was treated with 20 per cent sulphuric acid for 3 minutes which largely overcame contaminating organisms. The medium, a modification of the Loewenstein-Jensen medium, is as follows: (*1*) mineral salt solution: potassium phosphate KH_2PO_4 (A. R.) 2.0 gm., magnesium sulphate (A. R.) 0.2 gm., magnesium citrate 0.5 gm., asparagin 3.0 gm., distilled water 200 cc. Heat to dissolve. Boil or place in steamer for 2 hours and allow to cool over night. (*2*) Salt-starch solution: To each 200 cc. of the above solution is added 20 gm. of potato starch. Mix in and heat in water bath, stirring constantly for 15 to 20 minutes, allow to remain in water bath 1 hour at 56°C. (*3*) Egg fluid: Fresh hens eggs, washed in a 5 per cent soft soap solution and allowed to stand 1 to 2 hours in running water, are broken into a sterile cup and the yolk and white mixed. Mix thoroughly for 10 minutes and filter through sterile gauze into a sterile vessel. To each 200 cc. of the salt-starch solution, 500 cc. of egg fluid is required. (*4*) Seven cc. of 2 per cent solution of malachite-green in distilled water is added to the salt-starch-egg fluid mixture. Tube and inspissate.—*Demonstration of Tubercle Bacilli in Milk by Cultural Method, T. Ruddock-West & F. T. Alpe, J. State Med., September, 1936, xliv, 543.*—(*L. F. B.*)

Technique of Culture of Tuberculous Sputum.—The unreliability of negative results from examination of the ordinary stained direct smear limits its value, while guinea-pig inoculation, while most delicate, is expensive and entails delay. Two groups of concentration methods for sputum have been devised: (*1*) centrifugal concentration; (*2*) extraction by means of a suitable solvent. Pottenger has used the latter to advantage and the technique here described is a modification of his method. *Gasolene Concentration Test:* This, as described, consists of adding 0.5 sodium hydrate in equal volumes to 10 to 15 cc. of sputum in a marked tube, homogenizing by shaking mechanically, and after removing 5 cc. for culture, transferring to a water bath, decanting the supernatant fluid, diluting, adding 2 cc. petroleum ether, (B. P. 40° to 60° C.), again shaking, and pipetting off the ether emulsion onto clean sterile slides, which are dried on a hot plate washed, fixed and

stained with carbol-fuchsin by the Ziehl-Neelsen method. The medium used is a modification of Loewenstein's early formula to which has been added a small percentage of malachite-green, which makes an excellent background. It is an egg-glycerin-potato starch-asparagin medium, with mineral salts added. The 5 cc. removed in the concentration test are over-neutralized with 25 per cent sulphuric acid, the tube centrifuged, the acid poured off and the deposit washed with sterile water. Tubes of both plain and glycerinated media are planted, as glycerine inhibits bovine strains. Out of 100 cases in which *B. tuberculosis* could not be demonstrated by ordinary methods 37 positives were obtained by the gasoline concentration test and 49 by culture. Altogether 55 positives were demonstrated by one or both methods. These cases had at one time been positive on direct smear. Of 100 new cases, in whom tubercle bacilli had never previously been demonstrated, 9 were found positive by concentration and 14 by culture, or 17 by one or both methods. Of these 17, 15 were clinically tuberculous, 16 roentgenographically so, and 8 subsequently confirmed bacteriologically. Positives on concentration are reported when at least 3 bacilli are seen which conform rigidly to the morphology of *B. tuberculosis*. Before cultures are reported positive, there must be both macroscopic and microscopic evidence. Colonies may be visible as early as seven to ten days, and cultures should be observed at least twelve weeks before being pronounced negative.—*Concentration and Culture Methods in the Examination of Sputum for B. Tuberculosis, P. Edwards, A. Lynn & L. J. Cutbill, Tubercle, June, 1936, xvii, 391.*—(*A. P.*)

Glycerol and Carbohydrate Utilization by *M. Tuberculosis*.—The experiments reported had two objectives. The first was a study of the fate of glycerol in fluid medium cultures of *Mycobacterium tuberculosis*, the rapidity of its utilization and its end products. The second was to confirm and extend reports regarding the utilization of various carbohydrates. The glycerine metabolism of the tubercle bacillus is difficult to examine directly because of the lack of simple and accurate methods of glycerol analysis. In the present work the synthetic medium of Long and Seibert or a variation thereof was employed. The only organic matter present besides glycerol was 0.5 per cent asparagin and 0.5 per cent ammonium citrate. It was therefore possible to follow the course of glycerol utilization by a simple oxidation procedure in which all the organic matter present analyzed as glycerol. The carbohydrate metabolism of *M. tuberculosis* is unusual in that little or no acid is produced. The end products are chiefly carbon dioxide and water. Consequently only analytical methods are satisfactory for studies of its carbohydrate metabolism. The organisms used were three strains of human, three of bovine (including BCG) and one of avian tubercle bacilli. For the glycerol methods only Long's medium was used and for the carbohydrate methods Long's medium containing 2.5 per cent glycerol and beef-heart infusion broth containing 0.5 per cent glycerol. The sugars used as test agents were glucose, mannose, fructose, galactose, arabinose, xylose, lactose and maltose added to the media to make concentrations of about 0.45 per cent for monosaccharides and 0.70 per cent for disaccharides. It was found that human, bovine and avian tubercle bacilli utilized as much as 96 per cent of all oxidizable matter in Long's medium. This indicates that the glycerol is completely oxidized to carbon dioxide and water and that there is no appreciable accumulation of organic waste products. This in turn suggests that the decrease in pH which occurred was not caused primarily by the presence of organic acid. Quantitative analyses for reducing sugar indicated that human, bovine, and BCG types of *Mycobacterium tuberculosis* utilized all the sugars tested except lactose.—*Glycerol and Carbohydrate Utilization by Mycobacterium Tuberculosis, A. G. Wedum, J. Bact., December, 1936, xxxii, 599.*—(*J. S. W.*)

Isolation of Bovine Tubercle Bacilli.—The paucity of tubercle bacilli in smears prepared from the bronchial secretion of tuberculous cattle made it desirable to employ other methods to establish the diagnosis. For reasons of economy cultural methods were studied. It was found that while exposure to 15 per cent sulphuric acid for 5, 10 and 15 minutes destroyed many of the accompanying bacteria it did not destroy a spore-forming organism identified as *B. pseudoanthracis*. Neither neutralization of the acid-treated secretion with sodium hydroxide, nor treatment with 15 per cent sodium hydroxide inhibited the growth of this organism. Cultures of *B. pseudoanthracis*, and of cocci isolated from the bronchial secretion of cattle were suspended and treated with 5 per cent hydrochloric acid for 6, 16 and 24 hours, after which time they were neutralized, washed and cultured. It was found that the cocci were killed after 6 hours exposure and cultures of *B. pseudoanthracis* after 16 to 24 hours exposure to the acid. The bronchial

secretion from 56 freshly slaughtered tuberculous cattle was collected under sterile conditions, treated for 3 hours with 5 per cent hydrochloric acid and inoculated on Petragnani's medium and on Besredka's bouillon medium. Pure cultures of bovine tubercle bacilli were obtained in 89.5 per cent of the samples. Macroscopic colonies were noted in from 12 to 60 days after planting. Fifty samples of bronchial secretions were treated with 5 per cent hydrochloric acid for 3 hours and 50 samples were treated for 6 hours. The treated material was cultured on Petragnani's medium and on Besredka's medium. It was found that the secretions treated for 3 hours with hydrochloric acid yielded 10 per cent more positive cultures than the material treated for 6 hours. The authors conclude that bovine tubercle bacilli will withstand treatment with 5 per cent hydrochloric acid from 3 to 24 hours without interfering with their viability, and that positive results were obtained with this method in 98 of 100 specimens examined.—*Studien über die bovine Tuberkelbazillenkultur aus Lungenschleim tuberkulöser Rinder, H. Ritter & G. Nothdurft, Zentralbl. f. Bakt., December, 1936, cxxxviii, 84.*—(*J. D. A.*)

Intracerebral Inoculations of Tubercle Bacilli for Type Identification.—The polymorphism of tuberculosis of the central nervous system is so marked as to bring up the question whether the variation may not be dependent upon different types of bacilli. In consequence, intracerebral inoculations of various known laboratory strains were made into rabbits. The severity of lesions appeared to depend not upon the virulence of the strain, but on its original type, whether bovine, human or avian strain. Bacilli of the bovine type produced extensive caseous lesions, paralytic symptoms and death within a month. The human type, after producing a certain general debility without motor symptoms, became slowly destroyed or reduced to intracellular granules. When the animals were sacrificed later, in good health, only a small regressive or scarred lesion was found at the site of inoculation. Avian tubercle bacilli produced rapid death within two to three weeks, with localized lesions containing many bacilli and a generalized infection in all cases. Regardless of the difference in virulence of the avian bacilli previously determined by intravenous inoculation, the results were compatible. The intracerebral inoculation of BCG provoked not a single disorder in the rabbit. One animal sacrificed a month after inoculation showed a small, well-walled-off, nonnecrotic nodule in the centre of the hemisphere containing a few acid-fast bacilli. These results indicate that intracerebral inoculations might be helpful in the diagnosis of certain strains, particularly those isolated from cutaneous lesions, in which the character of the culture does not always indicate clearly the original type of tubercle bacillus. *Discussion by P. Armand Delille:* This intracerebral method of determining the type of the original strain of tubercle bacilli is particularly valuable in differentiating eugonic and dysgonic tubercle bacilli which are not typical. But one must remember that Negri has pointed out that certain strains do exist which are intermediary, in point of view of virulence for the rabbit, between human and bovine strains of tubercle bacilli.—*Sur la détermination du type originel des souches de bacilles tuberculeux par l'inoculation intracérébrale expérimental, I. Bertrand, J. Bablet & F. Bloch, Compt. Rend. Soc. Biol., January 16, 1937, cxxiv, 109.*—(*M. T. W.*)

Survival of Tubercle Bacilli.—It is generally believed that tubercle bacilli do not survive a thorough deprival of oxygen or water. Previous experiments and those now reported strongly negate this opinion. As before, avian tubercle bacilli were used in the experiments. In experiment A, masses of bacilli were placed in two Pyrex glass U-tubes containing magnesium in one arm, and subjected to as complete a deprival of oxygen and dessication as can be accomplished by physical and chemical methods. One tube yielded viable tubercle bacilli after 14-months' storage in the dark at room temperature. During all this period the high vacuum obtained at the start persisted. The bacilli removed were injected into rabbits and pigeons and also cultured, and always proved viable. The other tube gave similar results even after two years' storage. In experiment B, smaller tubes were used to contain the bacilli and the vacuum was obtained by replacing the oxygen with hydrogen and then evacuating the latter as completely as possible. Stored in the dark at 37°C. the tubes were opened after 1, 2, 5 and 12 months respectively and their bacillary content tested for viability. All tubes yielded viable and pathogenic bacilli. A noteworthy feature of the culture tests was that growth was but slightly retarded as compared with routine transplants from one stock culture tube to another. It is apparent that the severest deprival of oxygen and water yet accomplished does not cause the death of tubercle

bacilli.—*Survival of Oxygen and Water Deprival by Tubercle Bacilli, T. S. Potter, J. Infect. Dis., January–February, 1937, lx, 89.*—(*J. S. W.*)

Loss of Virulence of Bovine Strain.—Ordinarily the dysgonic type of bovine tubercle bacilli retains its virulence even on culture media over a long period of time. A strain of bovine tubercle bacilli, however, was isolated from the lymph node of a tuberculous cow in 1933 which behaved in quite a different manner from most bovine strains. After four years this strain was still dysgonic despite cultures on artificial media. Finally the strain developed slowly on potato medium and became dry and lightly pigmented. It had a low virulence for the rabbit. Cultures from organs of an animal inoculated with the strain invariably yielded a dysgonic growth. After growing the organism for four months in Besredka's medium, passing it through a rabbit and reinoculating it into guinea pigs and rabbits, it was found that the strain while still dysgonic had undergone an almost total loss of virulence. Only a few traces of a tuberculous infection could be found on autopsy of the inoculated animals.—*Perte de virulence d'une culture de bacilles tuberculeux de type bovin a caractère dysgonique, J. Valtis & F. van Deinse, Compt. Rend. Soc. Biol., January 9, 1937, cxxiv, 22.*—(*M. T. W.*)

Morphological Changes of Tubercle Bacillus.—The author describes the morphological and other changes which the tubercle bacillus undergoes during pneumothorax treatment. From the beginning of the treatment and until some time after the complete disappearance of the bacilli, he examined the sputa of 130 pneumothorax patients first daily, and at longer intervals later. He noticed that along with the increasing collapse of the lung and the clinical improvement of the patient, the bacillus shows some definite changes which he summarizes as follows: tendency to coagglutination in groups of 3, 4, 5 and even 20 elements so as to render their count difficult; phagocytosis by the polynuclear cells; prevalence of long forms with poorly colored bodies and intensely colored polar granules; reduction to minute granules; diminution and even almost complete disappearance of the acid-fastness. Together with these changes he also observed, in the majority of cases, an increase of the Schron-Micoli-Much granules and in 18 of the 23 cases in which a cytodiagnosis of the sputum was made, a progressive increase of the lymphocytes. The above changes are compared with the changes that the bacillus undergoes under unfavorable cultural conditions *in vitro*, and the importance of these phenomena in the course of pneumothorax treatment are discussed.—*Modificazioni morfologiche del micobatterio del tubercolo nel corso della tubercolosi polmonare, A. M. Bonanno, Giorn. di Batteriol. e Immunol., April, 1937, viii, 520.*—(*G. W. W.*)

R and S Forms of Acid-Fast Bacillus from Leprous Lesion.—A "rough" and a "smooth" form were isolated from a chromogenic acid-fast bacillus which had been recovered from a human leprous lesion. They differed morphologically and culturally and when given to rabbits at frequent intervals during a year, the "smooth" form proved to be more pathogenic in three rabbits than did the "rough" form in three other rabbits. The results obtained with the "S" form were as follows: marked emaciation after approximately seven months, subcutaneous nodules at the sites of inoculation, ulcerated nodules containing many acid-fast bacilli, many large phagocytic cells simulating lepra cells and containing acid-fast bacilli, marked fibrosis and generalized thickening of the blood vessels, and paralysis of extremities in two of the three rabbits. Less conspicuous changes were noted in the rabbits injected with the "R" form.—*Effect of "R" and "S" Forms of Chromogenic Acid-Fast Bacillus from Human Leprous on Rabbits, J. R. Kriz, Proc. Soc. Exper. Biol. & Med., January, 1937, xxxv, 546.*—(*F. B. S.*)

Polysaccharides of Tubercle Bacillus.—The polysaccharide portion of the human H37 strain of tubercle bacillus was obtained as a complex mixture of serologically active and inactive polysaccharides. One of the polysaccharides was relatively highly dextrorotatory, low in pentose and apparently contained magnesium palmitate in chemical combination. The other one had a low dextrorotation and was difficultly separable from larger amounts of similar material, combining both specificities, and, in general, showing relatively high pentose content. The fractions were built up chiefly of *d*-arabinose and *d*-mannose units in varying proportions. Analogous fractions were found in the polysaccharides of tuberculin.—*Specific and Non-Specific Cell Polysaccharides of a Human Strain of Tubercle Bacillus, H-37, M. Heidelberger & A. E. O. Menzel, J. Biol. Chem., March, 1937, cxviii, 79.*—(*F. B. S.*)

Biological Characteristics of Two Strains of Tubercle Bacilli from Blood of Tuberculous Children.—Biological studies were made on two atypical strains of acid-fast bacilli isolated from the blood of two young children who died of generalized tuberculosis. Both strains were non-pathogenic for rabbits and chickens, but one strain immunized a monkey to a subsequent infection with a known virulent strain of tubercle bacilli. The immunizing power of the second strain was not tested. Culturally the organisms resembled tubercle bacilli of the avian type. The colonies were smooth and cream colored. They grew only on glycerine medium. One strain when injected into the rabbit by intravenous inoculation produced an antiserum possesing a high titre in complement fixation. At the same time avian, human, bovine and other S strains gave fixation reactions of a very low titre. The other strain reacted specifically and with the same titre to antiserum of the first strain. Both strains resembled another atypical S variant isolated from the blood of a guinea pig which had been inoculated with the blood of a tuberculous patient.—*Caractères biologiques de deux souches de bacilles tuberculeux type S, isolées par culture directe du sang, chez de jeunes enfants morts de généralisation tuberculeuse, P. F. Armand-Delille, Compt. Rend. Soc. Biol., November 28, 1936, cxxiii, 877.*—(*M. T. W.*)

R and S Dissociates of Avian Tubercle Bacilli.—Avian tubercle bacilli at the time of isolation are typical R strains, but are easily dissociated *in vitro* into S variants. Recently isolated R and S variants have an equal virulence for chickens and rabbits. The S variant however loses its virulence for experimental animals after successive passage on culture media. One particular avian strain showed itself to differ from other avian strains in that the S variant retained its high virulence for chickens and rabbits even after passage on culture media at the end of four years. The R variant became less virulent for experimental animals than the S variant of the same strain. At the end of four years of passage on culture media the R variant had completely lost its virulence for laboratory animals. At the end of the forty-fourth passage of the S variant, a second R strain (R_2) was isolated. This strain showed a lesser degree of virulence for susceptible animals than the S strain from which it was dissociated. The original S strain produced death in the chicken in doses from 10 mgm. to .000,01 mgm. The R_2 strain produced discrete lesions of tuberculosis in chickens in doses 0.1 to .01 of mgm. Cultures made from the organs of the chickens inoculated with this R_2 strain at first yielded both R and S colonies. After forty-one passages on Loewenstein's medium, R variants greatly outnumbered the S variants of which there were two colonies out of twenty-four culture tubes. After the fifty-second passage on Loewenstein's medium the R strain became completely avirulent for chickens, rabbits and guinea pigs. In order to test the stability of this R variant, the bacillus was recovered from an inoculated chicken, diluted to various degrees and cultured on Loewenstein's medium. All the cultures yielded typical R colonies. Thus it was shown that, contrary to the usual observation, the R variant lost its virulence for susceptible laboratory animals and remained typically R in character, both *in vivo* and *in vitro.*—*Perte du virulence et stabilité de la variété R d'une souche de bacilles aviaires observées après cinq années de passage in vitro sur pomme de terre glycerinée, A. Saenz, Compt. Rend. Soc. Biol., February 27, 1937, cxxiv, 704.*—(*M. T. W.*)

Mutations of Tubercle Bacilli.—An attempt was made to repeat the work of Sartory, and Sartory and Meyer regarding the effect of the precipitate derived from Koch's tuberculin and sulphoguaiacolic acid upon growth of tubercle bacilli, using their media and various modifications of the Loewenstein type of medium. A number of variations in the media were made as well, and in none of them was a diminution in virulence of the organisms noted. One type of medium appeared to produce a more virulent organism. No genuine evidence of alteration in morphology of subcultured organisms was noted except as occur on all media with an aging of the culture. Attempts to obtain pure cultures of chromogenic variants were made, but the cultures tended to contain more or less white variants. Animal inoculations with organisms from the various media after at least 6 subcultures showed that some attenuation of virulence was obtained. The most attenuated organisms had been grown upon "Nordalin" containing media. It also appeared that chromogenic variants were more virulent than the white variants. It is not yet possible to confirm the findings in the work upon the effect of sulphoguaiacolic acid precipitate from tuberculin upon the growth of tubercle bacilli.—"*Mutations*" *Occurring in the Tubercle Bacillus upon Culture, D. Haler, J. State Med., February, 1937, xlv, 74.*—(*L. F. B.*)

Effect of Methyl and Acetone Extracts and Tuberculin upon Atypical Acid-Fast Bacillus.—An atypical acid-fast bacillus was isolated from a malignant lymphogranuloma. It was avirulent when originally isolated for the rabbit and guinea pig when inoculated in large doses. The pathogenic properties were increased *in vitro* by growing the organism in Sauton's medium to which had been added tuberculin, acetone and methyl extracts of Koch's bacilli. *In vivo* the pathogenic power was augmented to a point where it produced rapid death to the rabbit by intravenous inoculation of the bacilli in a mixture of those three extracts. Perhaps this may be explained by the theory of dissociation of the microörganism into an aggressive agent preëxistent to its saprophytic state in the rabbit. The acetone extract and the tuberculin separately enhanced its virulence but to a lesser degree. This organism behaved in a manner somewhat like tubercle bacilli isolated by Nègre from inoculated animals treated with acetone extract.—*Exaltation du pouvoir pathogènic, pour le lapin, d'un bacille tuberculeux peu virulent, par action in vitro et in vivo d'extraits acétoniques, méthyliques et de tuberculine, F. Le Chuiton, J. Sabrazes & J. Pennaneac'h, Compt. Rend. Soc. Biol., November 7, 1936, cxxiii, 581.*—(*M. T. W.*)

Increase of Tolerance to Tuberculin by Vitamin C.—Daily injections of crystalline vitamin C increased the tolerance of tuberculous guinea pigs to repeated large doses of tuberculin. No evidence was obtained for a direct inactivation of tuberculin by vitamin C. In most cases those animals treated with ascorbic acid showed at autopsy the presence of reducing substances in their adrenals, whereas the untreated tuberculous animals which died of tuberculin shock showed none. At autopsy most of the treated animals showed more extensive tuberculosis than did the corresponding ascorbic acid treated animals.—*Effect of Crystalline Vitamin C (Ascorbic Acid) on Tolerance to Tuberculin, M. Steinbach & S. J. Klein, Proc. Soc. Exper. Biol. & Med., October, 1936, xxxv, 151.*—(*F. B. S.*)

Persistence of Sensitivity to Tuberculin in Culture Cells.—It has previously been shown that mesenchymal cells from tuberculous guinea pigs exhibit a characteristic sensitivity to the toxic action of tuberculin when tested in tissue culture. This sensitivity persisted in cultures that had been transplanted several times. In order to eliminate the possibility that tissue fluids, carried over with the explants, were responsible for the persistence of the cellular sensitivity, it seemed desirable to determine whether growths derived from single cells, or from small aggregates of cells, and comparatively free from tissue fluids of the tuberculous environment, would retain their hypothetical inherent sensitive state. The cellular suspensions were obtained from normal and tuberculous guinea pigs by the intrapleural injection of molten parowax and consisted almost entirely of mononuclear cells, lymphocytes, monocytes and clasmatocytes. The cells were mostly isolated, with only occasionally small clumps of microscopic size. These mononuclear cells grew well on a special tissue culture medium, some developing as typical migrating macrophages, and others becoming transformed into typical fibroblasts. The types of cells and extent of proliferation of mononuclear cells from the tuberculous and the normal animal were essentially the same when grown in normal media. When old tuberculin was incorporated in the media in concentrations of 1 to 300 and 1 to 600, the mononuclear cells from normal animals were only slightly inhibited in their growth. Mononuclear cells from tuberculous animals, however, were distinctly inhibited (growth) by old tuberculin in the two concentrations used. Cellular sensitivity to tuberculin was plainly present. To determine the persistence of this sensitivity, transplantation experiments were done in which the cells were originally obtained from a guinea pig infected with the strain R1 tubercle bacillus and grown on normal media for 8 days. A transplant from this strain together with control transplants (originally from normal animals) were transferred to flasks containing normal media. Similar transplants were transferred to a flask containing media and tuberculin (1–300). The normal fibroblasts were only slightly affected by the presence of the tuberculin whereas the cells originally derived from the tuberculous animal were markedly affected. They became very dark in color, heavily granulated and swollen. A marked sensitiveness to tuberculin was present on the 6th day after transplantation, or on the 14th day after the original explantation. A second transplantation was done from transplant one using the fibroblasts growing on normal medium. This transplant was divided between normal media and the tuberculin-containing media. On the 6th day after the second transplantation or 22 days after the original explantation the sensitivity to tuberculin of the cells of

tuberculous origin persisted. A third transplantation was then carried out, and even on the 29th day after the original explantation fibroblasts derived from the original sensitive cells still displayed sensitivity to tuberculin as evidenced both by microscopic cellular changes and by quantitative inhibition of fibroplastic growth. The initial growth energy of the fibroblasts decreased during the last period so no further transplanting was done. In these experiments the presence of tissue fluid that might be carried over with the explants and thus be responsible for cellular sensitivity *in vitro* is pretty well ruled out. The tissue-fluid toxin would appear to be too diluted to exert any demonstrable effect. On the other hand, there is convincing evidence that sensitivity is an inherent characteristic of cells from tuberculous animals. This inherent cellular characteristic persisted after prolonged culture *in vitro* and was still demonstrable after three transplantations, and over a period of 29 days. The nature of this sensitivity is not understood. If the thesis that allergy in tuberculosis is of the nature of an antigen-antibody union in which the antibody is bound to the cell is accepted, then cells grown for a prolonged period *in vitro*, by repeated transplantations in the absence of antigen, would have to elaborate continuously sensitizing antibodies. There is no conclusive proof, however, that tuberculin allergy is the result of an antigen-antibody reaction, and these experiments fail to throw further light on this problem.—*Tissue Culture Studies on Bacterial Hypersensitivity. III. The Persistence in Vitro of the Inherent Sensitivity to Tuberculin of Cells from Tuberculous Animals (with two plates), J. K. Moen, J. Exper. Med., December 1, 1936, lxiv, 943.—(J. S. W.)*

Histology of Intracutaneous Reaction to Tuberculin in Cattle.—At present the intracutaneous tuberculin test has superseded all others as a means of disclosing tuberculous infections not only in cattle, but in other domestic species of animals as well. There is no report available concerning the histological changes which the reaction produces in cattle. The present article has to do with the character of the local alterations in tissues and the cellular response in cattle showing a positive reaction to tuberculin administered intracutaneously and the correlation, if any, between the character of the histological reaction and the extent or severity of tuberculous infection as ascertained at necropsy. The material used for the study was obtained from two groups of animals consisting of (1) four calves, two having received bovine tubercle bacilli, one avian tubercle bacilli and the fourth animal, a normal calf, utilized as a control and (2) sixty-six head of adult cattle which were members of thirty-three separate farm herds. The group one animals received the usual intracutaneous diagnostic dose (0.1 cc.) of mammalian tuberculin in one caudal fold and the same amount of avian tuberculin in the other. All the group two animals received the usual dose of mammalian tuberculin intracutaneously in the tissues of a caudal fold. The tissues which were the sites of local tuberculin reaction were removed for study at the time the results of the tuberculin tests were recorded (70 animals). In the majority of instances this was approximately seventy-two hours after the tuberculin had been injected. After the reacting areas were excised, the animals were slaughtered and subjected to a careful postmortem examination for lesions of tuberculosis. Results: *1:* The reaction to tuberculin in cattle is a rather definitely cellular response, predominantly histiocytic and showing a predilection for the perivascular and perineural areas of the derma. *2:* While the local reactive process is confined in most instances to the papillary and reticular zones of the derma it may, if the inflammatory response is severe, extend into the tissues of the subcutis. *3:* There is no correlation between the intensity of the histologic alterations and the results of the tuberculin test as observed clinically. *4:* There are no distinguishing criteria in the histologic picture to indicate whether demonstrable lesions of tuberculosis are present in a given animal. *5:* In all cattle, in which these characteristic changes occur, the uniformity of the reaction suggests the possibility of the existence of a common or closely related sensitizing agent.—*Histologic Features of the Intradermic Reaction to Tuberculin in Cattle, W. H. Feldman & C. P. Fitch, Arch. Path., October, 1936, xxii, 495.—(J. S. W.)*

Tuberculin in Blood of Rabbits in Course of Yersin Type of Tuberculosis.—The Yersin type of acute toxic tuberculosis in rabbits with sudden death of the animals following immediately the intravenous inoculation of avian or bovine tubercle bacilli or, on the other hand, succumbing to sudden death some weeks later by shock in animals in apparently good health, has been described previously. The cause of this sudden death was not known. Boquet and Laporte have demonstrated the solubility of tuberculin in serum. It seemed possible that it

might be the tuberculin coming from the large number of bacilli which caused the death by shock in the course of tuberculosis of the Yersin type. This type of death might be considered as an allergic phenomenon analogous to that of Bail. Experiments were undertaken to try to determine whether tuberculin was present in the bloodstream in the final stages of experimental tuberculosis of the Yersin type. For convenience the serum taken from these animals was called Y-serum. Seven tuberculous guinea pigs were given intracutaneous inoculations of Y-serum, five of which showed positive reactions. Twenty-seven more tuberculous guinea pigs were given normal serum and Y-serum with the result that they all reacted with equal intensity to both sera. In one case an animal showed a haemorrhagic reaction to Y-serum while normal serum and tuberculin gave only faintly positive reactions. The reaction to the normal serum is explained by the hypersensitivity of the tuberculous animal to foreign protein. Consequently an attempt was made to remove the albumen by heat. More tuberculous animals were skin tested with avian tuberculin, normal and Y-serum from which the albumen had been precipitated. All the animals reacted to the tuberculin but not a single one reacted to either serum. It is possible that the heat had removed the tuberculin as well as the albumen. Since the skin tests presented negative results, intraperitoneal inoculations were attempted. Forty-two tuberculous guinea pigs were given fresh Y-serum, twelve were given normal serum, ten were injected with fresh normal serum, and three control guinea pigs were given fresh normal serum, all intraperitoneally. Of the first lot, eight animals died of shock. In the second lot one died of shock. None of the control guinea pigs died. For comparison four tuberculous guinea pigs were given intraperitoneal inoculations of tuberculin, two of which died of shock. Four more tuberculous guinea pigs were given avian tuberculin intraperitoneally, none of which died. It appeared that the mortality from shock was more common in the guinea pigs inoculated with Y-serum than with animals which received normal serum. This fact might be considered an indication of tuberculin-like substances in the serum. However a final experiment was carried out. Twenty-nine tuberculous guinea pigs were given intraperitoneal inoculations of Y-serum from which the albumen had been precipitated. Three control guinea pigs received normal but precipitated serum. Only one animal died of shock, illustrating conclusively that in the former series death was due to protein shock and not to the presence of tuberculin in the Y-serum. From these series of experiments it can be concluded that there is no evidence supporting the theory that the blood serum of rabbits with the Yersin type of tuberculosis contains tuberculin.—*Essais de mise en evidence de tuberculine dans le sérum des lapins au cours de la tuberculose "Yersin", F. van Deinse & M.-A. Domanski, Compt. Rend. Soc. Biol., January 23, 1937, cxxiv, 238.*—(*M. T. W.*)

Allergy in Guinea Pigs following Inoculation of Dead Tubercle Suspended in Oils.—Experiments have been performed demonstrating the allergizing effect of killed avian tubercle bacilli and paratubercle bacilli suspended in oil of vaselin. Guinea pigs were given subcutaneous inoculations of killed bacilli suspended in animal, vegetable and mineral oils, in the egg yolk and in physiological salt solution. The animals were tested with tuberculin in varying doses and at various intervals. The allergic response differed depending upon the medium in which the bacilli were suspended. Bacilli in lanolin and egg yolk did not alter the allergizing effect of dead bacilli. Normal saline suspensions of dead bacilli produced a faint allergic response. Bacilli in vegetable oils exerted an increased allergic reaction in the animals almost equal to that produced by bacilli in vaselin oil. Guinea pigs inoculated with bacilli in vaselin oil, however, showed from the sixth day after inoculation a strongly positive reaction to tuberculin which became necrotic on the fifteenth day. The intensity of the reaction was four times greater than with living and virulent bacilli suspended in physiological salt solution.—*Degré d'allergie conféré au cobayes par l'inoculation de bacilles tuberculeux morts enrobés dans des excipients gras d'origine végétale ou animale, A. Saenz, Compt. Rend. Soc. Biol., January 30, 1937, cxxiv, 338.*—(*M. T. W.*)

Allergic Response following Inoculation with Oil Vaccines.—It has been shown that guinea pigs living in old experimental cages may become spontaneously infected with acid-fast bacilli which present certain allergic properties analogous to avian tubercle bacilli but different pathogenic properties. Likewise it has been shown that both heat-killed avian and human tubercle bacilli suspended in oil of vaselin have the power to increase the allergic sensitivity in experimental animals. It is possible to differentiate these two

strains by this allergic reaction. It was thought that, by using the same technique, the acid-fast bacilli isolated from spontaneously infected guinea pigs could be differentiated from true avian tubercle bacilli. Guinea pigs were inoculated with two strains of the newly isolated acid-fast bacilli, killed by heat and suspended in vaselin oil. These animals were tested side by side with animals similarly inoculated with dead avian and human tubercle bacilli suspended in the oil. Control animals inoculated with killed bacilli suspended in physiological salt solution were observed at the same time. All the animals were tested at intervals varying from twenty-five days to eight months after inoculation with tuberculin in dilutions from 1:10 to 1:2,000. The animals treated with dead bacilli suspended in saline solution either did not react at all or reacted with a small papule. The animals treated with dead human tubercle bacilli or with the newly isolated acid-fast bacilli suspended in vaselin oil showed reactions nearly twice as intense as the animals inoculated with the killed avian tubercle bacilli. The former animals reacted to tuberculin in a dilution of 1:2,000 with a necrotic or haemorrhagic area, while the animals treated with the avian tubercle bacilli reacted to the tuberculin with only a slight infiltration. It is thus possible to distinguish by the allergic response the acid-fast bacilli isolated from spontaneously infected guinea pigs from avian bacilli which they closely resemble culturally.—*Caractères des réactions allergiques déterminées par des bacilles morts isolés de cobayes neufs et enrobés dans l'huile de vaseline, A. Saenz, Compt. Rend. Soc. Biol., March 13, 1937, cxxiv, 887.*—(*M. T. W.*)

Delay of Dispersion of Tubercle Bacilli of Reinfection.—In view of the fact that dead tubercle bacilli suspended in vaselin oil produce a marked augmentation of the allergic response in guinea pigs the question arose whether this increased allergic manifestation is accompanied by a concomitant resistance toward an experimental infection. Guinea pigs treated with the oily suspension of dead bacilli were given inoculations into the inguinal region of virulent tubercle bacilli of a bovine strain when their allergic manifestations were at a peak, about fifty-eight days later. A second series of animals was similarly treated with dead bacilli but suspended in physiological saline. These were inoculated with the same strain of bovine tubercle bacilli forty-eight days later. Control untreated guinea pigs were likewise given inoculations of the same strain. At intervals from two to twenty-six days the animals were sacrificed and their inguinal lymph nodes and spleens were cultured for tubercle bacilli. A second series of animals was treated in the same manner with dead tubercle bacilli suspended in both vaselin oil and in physiological salt solution but were inoculated into the inguinal region with tubercle bacilli of a human strain of known virulence. A control series inoculated but untreated was observed at the same time. These animals were sacrificed at varying intervals and their organs cultured. From these experiments it was shown that in the control animals tubercle bacilli of both human and bovine strains could be demonstrated in the neighboring lymph nodes five days after inoculation; the spleen was contaminated toward the twelfth day following the infection. In the group of animals treated with the saline suspension of dead bacilli, tubercle bacilli were recovered from the lymph nodes and spleen at about the same time as in the control animals, but the number was considerably less. In the animals treated with the oily suspension of dead bacilli, the bacilli of the reinfection remained localized at the site of inoculation until the seventh day after the infecting injection at which time they commenced to invade the neighboring lymph nodes where they rapidly multiplied. At the end of the twenty-sixth day when these experiments were terminated no tubercle bacilli could be demonstrated in the spleens of these animals. It is thus shown that inoculations of dead tubercle bacilli suspended in oil of vaselin not only produce a marked allergic response to tuberculin but hold the bacilli of reinfection in check at the site of inoculation, thus retarding their dispersion to the surrounding lymph nodes and the spleen.—*Retard de la dispersion des germes de surinfection chez des cobayes préparés avec des bacilles tuberculeux mort enrobés dans de l'huile de vaseline, A. Saenz, Compt. Rend. Soc. Biol., April 17, 1937, cxxiv, 1161.*—(*M. T. W.*)

Dissemination of Tubercle Bacilli in Normal, Allergic and Desensitized Guinea Pigs.—Small amounts of tubercle bacilli of a eugonic human type were injected into the cervical lymph node of normal guinea pigs. Other guinea pigs were first infected with a dysgonic bovine bacillus subcutaneously and then, either during the subsequent allergy or after preliminary desensitization with tuberculin, were reinfected in the cervical lymph node with small doses of a human eugonic tubercle bacillus

just like the normal animals. The rate of dissemination of the eugonic bacilli to the internal organs and lymph nodes was determined by cultures on Loewenstein's medium. The colony characteristics of the two strains were different. It was found that in normal guinea pigs the internal organs were invaded by the bacilli in three days. In the allergic animals this invasion was delayed until the fifth week. In the allergic and desensitized guinea pigs the invasion of the internal organs was delayed for seven weeks. The macroscopical and microscopical appearance of the tuberculous lesions in these animals, killed up to eighty days after reinfection, showed more extensive and caseous lesions in 50 per cent of allergic sensitive than in the allergic desensitized animals. It is concluded that desensitization leaves the immunity intact and reduces the tendency for extensive caseous lesions. A review of the literature on allergy and immunity in tuberculosis is also presented.—*Allergy and Immunity in Experimental Tuberculosis. I. Dispersion of Tubercle Bacilli in the Normal Allergic and Anergic (Desensitized Guinea Pig), K. E. Birkhaug, Acta tuberc. Scandinav., 1937, xi, 25.—(M. B. L.)*

Sensitivity of Tissue Cultures to Tuberculin.—Tuberculin, in proper concentration, has a selective toxic effect on cells from tuberculous animals. This phenomenon was studied by the use of tissue culture methods. The tissues were obtained from rabbits and guinea pigs infected with bovine tubercle bacilli (B1) and human tubercle bacilli (H37 and R1) respectively. Normal rabbit plasma with rabbit embryo extract was used for the growth of rabbit tissue and normal guinea-pig plasma plus guinea-pig spleen extract was employed for guinea-pig tissues. Old Tuberculin was added to the media in amounts so that the final dilution of tuberculin in the media was from 1–200 to 1–300. This concentration has but slight inhibitory effect on normal cells. The tissue for culturing was obtained mostly from the spleens of the animals. Qualitative and quantitative estimations of the effect of tuberculin on sensitive and normal cells were made daily. The two important quantitative factors studied were the cytotoxic index which is the rate of growth in media containing tuberculin as compared with growth in plain media and the comparative cytotoxic index which is the cytotoxic index of tuberculin on test explants compared with the cytotoxic index of tuberculin on normal explants. Cells from animals infected either with the highly virulent H37 or with the low virulent R1 strains showed similar degrees of sensitivity to the tuberculin. This marked sensitivity persisted in cells from R1 infected animals at least as long as four months after infection when the only evidences of disease present were small abscesses at the sites of inoculation. Other cytotoxic substances than tuberculin were introduced into the media in dilutions having but slight effect on normal cells. These substances also had little or no effect on tuberculin sensitive cells. Furthermore tuberculin sensitive cells were found to maintain their sensitivity after two transplants during which time many generations of cells must have resulted by proliferation on artificial culture. Tubercle bacilli never could be demonstrated in these explants hence it seems improbable that the growth of the bacilli in the explants is the explanation for the persistence of cellular sensitivity to tuberculin *in vitro*. However, the body fluids carried over with the explants may diffuse into the media as the explants grow, and may possibly play a rôle in sensitizing the newly grown cells. *Summary and Conclusions: 1:* A high degree of cellular sensitivity to tuberculin toxicity was demonstrated when explants from tuberculous animals were grown in media containing that substance. *2:* Similar degrees of sensitivity were noted in cells derived from animals infected with either virulent or relatively low virulent strains of tubercle bacilli. *3:* The specificity of the tuberculin cytotoxicity was proved by testing with other bacterial cytotoxic materials. *4:* Tuberculin sensitive cells grown *in vitro* in normal media showed, when tested with tuberculin, persistence of this cellular sensitivity through several transplantations during which time many new generations of cells developed. *5:* There was a depression of the initial growth energy of explants from animals during the toxic phase of the disease. During the healing stage the initial growth energy returned to normal although marked sensitivity to tuberculin persisted. *6:* The degree of cellular sensitivity to tuberculin *in vitro* did not parallel the acuity of the infectious process but represented a more or less permanent acquired characteristic impressed on the cell as a result of the infection.—*Tissue Culture Studies on Bacterial Hypersensitivity. I. Tuberculin Sensitive Tissues, J. K. Moen & H. F. Swift, J. Exper. Med., September 1, 1936, lxiv, 339.—(J. S. W.)*

Significance of Tuberculin Test.—In 1926 the authors published the results of

tuberculin testing of school children in the city of Minneapolis, which showed that, of 2,118 tested, 47.33 per cent reacted positively. During 1936, 4,549 children were retested in the schools in which testing had been done ten years before. There has been a sharp decrease in the percentage of children reacting positively to the test, indicating that the environment of the present school children has been very much better so far as exposure to tubercle bacilli is concerned, than was that of the children in the same age period ten years ago. Of the 4,549 children tested in 1936, only 18 per cent were found to be positive reactors. In many parts of the country, the number of positive reactors among children and young adults is decreasing. In these places, programs have been in effect to reduce definitely the number of communicable cases of tuberculosis through isolation, treatment and other measures. Although the reporting of persons who do not show any evidence of tuberculosis except the positive tuberculin reaction is strongly opposed at the present time, it must eventually be considered as an important part of a tuberculosis control program. The X-ray film of the chest fails to reveal the location of the primary complex in 75 per cent or more. Moreover, knowing the location of the complex is of no material assistance to the clinician. The authors no longer recommend making X-ray films of the chests of children except for the detection of developing reinfection or the clinical type of tuberculous lesions. This type of lesion is found in the chests of children who are positive tuberculin reactors only once in 2,000 or 3,000 examinations. There are other age periods in life when films reveal much more evidence of clinical tuberculosis. During the high-school age one may expect to find evidence of developing clinical disease in one in every 500 to 800 positive reactors. In the college age period a larger number of positive reactors is found to have developing or well established clinical disease, whereas in the twenties and thirties one may find one case of clinical tuberculosis in every 100 or 200 positive reactors. Close observation is important for every child who reacts positively to the tuberculin test as soon as young adult life is reached, since the fact has been well established that in a good many such children clinical disease develops during adult life. In a group of children (average age about 8 years) reacting positively to the tuberculin test in 1921–1922, the authors found that approximately 10 per cent have already developed clinical tuberculosis. Therefore, all these children who have reached the period of adolescence and all others as soon as they approach this period should have annual X-ray examinations of their chests. In this age period and thereafter the X-ray film is indispensable in the tuberculosis control program. By such a program of observation, practically all children who develop clinical disease will have it detected before symptoms are present and before it has become communicable.—*Significance of the Tuberculin Test, F. E. Harrington, J. A. Myers & N. M. Levine, J. Am. M. Assn., April 17, 1937, cviii, 1309.*—(*G. L. L.*)

Hypersensitiveness and Antibodies in Tuberculous Rabbits.—This study has to do with the relationship of tuberculin skin sensitiveness to antibody formation and their relationship to the tuberculous infection. Rabbits were infected with virulent bovine bacilli, tested with intracutaneous injections of tuberculin and the antibody content of their blood determined at weekly intervals throughout the course of the disease. The rabbits received from 0.001 to 0.000,001 mgm. of tubercle bacilli either by the intravenous or intratracheal route. For skin-testing 40 mgm. of a potent tuberculin (Old Tuberculin?) was injected intracutaneously. The antigen used for the complement fixation (antibody determination) was made from the infecting strain of bovine tubercle bacilli. Two groups of rabbits survived for up to 5 months and a third group, more heavily infected, up to 3 months. Skin sensitiveness to tuberculin appeared usually in 3 to 4 weeks and disappeared in all rabbits several weeks before death. The complement fixation reaction usually became positive by the 4th week and the maximum level persisted until death. A comparison of the curves of hypersensitiveness and antibody formation shows the following: The development of tuberculin sensitiveness as a rule preceded the formation of antibodies and the maxima of the two curves did not coincide. The tuberculin skin sensitiveness disappeared several weeks before death, while the antibodies persisted in the blood until the animals became moribund or died. With one exception, the intensity of the tuberculin reaction and antibody formation was dissimilar in the individual rabbits. In interpreting the disappearance of tuberculin skin reactions, it should be noted that these tuberculous rabbits are still quite sensitive to tuberculin when given subcutaneously. Skin sensitiveness may be lost, but the systemic reaction is amply present. In correlating the tuberculin tests with the antibody titration, it should be taken into consideration that in these tests two different preparations were used. It is difficult to compare the potency of these preparations:

the suspension of heat-killed tubercle bacilli (antigen) and the tuberculin. Tuberculin preparations are feeble (very) "antigens" in the complement fixation test.—*Hypersensitiveness and Antibody Formation in Tuberculous Rabbits, J. Freund, E. H. Laidlaw & J. S. Mansfield, J. Exper. Med., October 1, 1936, lxiv, 573.*—(*J. S. W.*)

Splenectomy in Rabbits Immunized and Reinfected with Avian Tubercle Bacilli.—The Yersin type of tuberculosis is characterized by the marked effect in the spleen of experimentally infected animals. Frequently the spleen is the only organ in which any gross lesions develop. It has already been reported that rabbits can be immunized with heat-killed avian tubercle bacilli to living bacilli of the same strain. A series of experiments was made to determine the possible rôle of immunity which the spleen played in immunized and reinfected animals. Splenectomized rabbits and normal rabbits were immunized with heat-killed avian tubercle bacilli composed of five different strains. Normal and splenectomized, but nonimmunized rabbits were observed side by side with the immunized animals. Due to the immunizing doses only three normal and two splenectomized rabbits remained alive. Each of these rabbits was given intravenous inoculations of the avian tubercle bacilli from which the vaccine had been made. All the immunized rabbits resisted the experimental infection. The splenectomized control rabbits died of a tuberculous infection as did the normal control animals. The immunized rabbits and the rabbits from which the spleens had been removed died of spontaneous nontuberculous infections three to four months later. At autopsy no tuberculous lesions could be found in any of the animals. It was not possible to recover tubercle bacilli from cultures of their organs. In the group of animals which were not immunized the splenectomized rabbits did not develop tuberculosis any more rapidly than did the normal rabbits.—*Essais d'immunisation de lapins splénectomisés par des bacilles tuberculeux de type aviaire, tués par chauffage, F. van Deinse, Compt. Rend. Soc. Biol., March 13, 1937, cxxiv, 893.*—(*M. T. W.*)

Production of Tuberculosis Antibodies in Superimposed Infections with Bang's Bacilli.—The fact has previously been established that tuberculosis favors the development of agglutinins in a superimposed brucella infection. Studies were undertaken to determine the effect of an infection with Bang's bacilli on the production of specific tuberculosis antibodies in a tuberculous infection. Tuberculized guinea pigs and rabbits were inoculated with Bang's bacilli. The animals had been previously tested for tuberculosis agglutinins with negative results. The brucella infection failed to raise the titre of the tuberculosis antibodies in either group of experimental animals.—*Recherches sur les anticorps antituberculeux chez les cobayes tuberculeux, surinfectés par le bacille de Bang, W. Sarnowieg, Compt. Rend. Soc. Biol., November 21, 1936, cxxiii, 775.*—(*M. T. W.*)

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